Scandinavian Journal of Gastroenterology, 2008; 43: 1311–1314

informa
healthcare

ORIGINAL ARTICLE

Clinical response to gluten withdrawal is not an indicator of coeliac disease

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Abstract

Objective. Although the diagnosis of coeliac disease requires specific histological and serological findings, patients considered to be affected by coeliac disease only on the basis of clinical improvement after gluten withdrawal are commonly referred to our outpatient clinic. The objective of this study was to investigate whether the clinical response of gastrointestinal symptoms to gluten withdrawal and subsequent dietary re-introduction could be an indicator of the presence of coeliac disease. ***Material and methods.*** From December 1998 to January 2007, 180 patients on a gluten-free diet because of a diagnosis of coeliac disease not based on proper diagnostic criteria came to our out-patient clinic. In 112 of these patients, gluten was re-introduced into their diet. Subsequent duodenal biopsies and endomysial antibodies confirmed the diagnosis of coeliac disease in 51 of them. The relationship between improvement/worsening of symptoms and withdrawal/re-introduction of dietary gluten was analysed. ***Results.*** Gastrointestinal symptoms improved in 64.7% of coeliac patients and 75.0% of non-coeliac patients after gluten withdrawal (χ^2 test, p =NS). Gluten re-introduction was followed by clinical exacerbation in 71.4% of coeliac patients and 54.2% of non-coeliac patients (χ^2 test, p =NS). The positive predictive value for clinical improvement after gluten withdrawal was 36%; the positive predictive value for clinical exacerbation after gluten re-introduction was 28%. ***Conclusions.*** Clinical response to either withdrawal or re-introduction of dietary gluten has no role in the diagnosis of coeliac disease.

Key Words: *Coeliac disease, endomysial antibodies, gliadin, gluten-free diet, tissue transglutaminase antibodies*

Introduction

Coeliac disease (CD), a gluten-sensitive chronic enteropathy, is characterized by a wide clinical presentation, ranging from severe forms of malabsorption to subclinical or silent forms [1,2]. The diagnosis of CD is based on small-intestinal mucosal abnormalities that recover after removal of gluten from the diet and on coeliac antibodies [3]. Although the original European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) criteria allowed the diagnosis of CD in patients with a flat duodenal biopsy and in whom dietary gluten removal was followed by symptom improvement [4], it is not clear whether a clinical response after gluten withdrawal can be considered to be a clinical indicator of CD *per se*.

During the past few years we had the impression that many patients, as well as some doctors, consider symptom relief after gluten withdrawal not only as an indicator of CD but also as an appropriate diagnostic criterion for CD. In our clinical practice we frequently encounter patients who complain of gastrointestinal symptoms, possibly due to CD, who have not undergone duodenal biopsies or coeliac antibody testing but who have nevertheless already started a gluten-free diet (GFD). Since clinical improvement on a GFD does occur often, these patients are firmly convinced that they are affected by CD and come to our centre, one of the few gastroenterology units in the Lombardy region where patients can obtain a GFD certificate and regional health-service tax exemption. In order to confirm the diagnosis of CD, in our clinical practice

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(Received 26 March 2008; accepted 7 May 2008)

ISSN 0036-5521 print/ISSN 1502-7708 online
DOI: 10.1080/00365520802200036

we advise all these patients to re-introduce gluten into their diet and then to undergo the proper serological and histological investigations.

A few years ago it was shown that a history of abdominal symptoms after ingestion of cereals is not specific for CD [5]. The aim of our study was to investigate whether clinical improvement after the start of a GFD could be taken into account as a clinical indicator of CD.

Material and methods

From December 1998 to January 2007, 705 patients presumed to be affected by CD attended our outpatients' clinic for the first time. We examined all their clinical notes and we selected all those patients who were already on a GFD despite a diagnosis of CD not based on duodenal biopsies showing a certain degree of villous atrophy and positive endomysial or tissue transglutaminase antibodies. So, to either confirm or exclude the diagnosis of CD, we proposed a dietary gluten re-introduction followed by duodenal biopsies and endomysial antibody testing in 180 of them. The clinical records of those patients accepting this diagnostic procedure were analysed.

As far as dietary gluten re-introduction is concerned, we normally recommend starting with a daily slice of bread, progressively increasing this to the normal Italian gluten intake. In these patients, we tend to do duodenal biopsies and test for coeliac antibodies after at least a few weeks or earlier if patients cannot tolerate the symptoms. We routinely take four duodenal biopsies in the second part of the duodenum; biopsies are always oriented on cellulose nitrate paper, formalin fixed and paraffin embedded. Serum endomysial antibodies are tested by indirect immunofluorescence on monkey oesophagus.

According to the results of our re-investigations, those patients found to have a certain degree of villous atrophy and positive endomysial antibodies were considered to be affected by CD, whereas CD was excluded in those patients with a normal duodenal biopsy and negative endomysial antibodies while on a gluten-containing diet.

A χ^2 test was used to compare the improvement in gastrointestinal symptoms in the two groups when on a GFD. Analogously, a χ^2 test was used to compare the relapse of gastrointestinal symptoms following gluten re-introduction between coeliac patients and non-coeliac patients.

Results

In 180 out of 705 patients the diagnosis of CD could not be confirmed; 117 out of these 180 patients agreed to undergo dietary gluten re-introduction and then to repeat the duodenal biopsies and endomysial antibody testing. Clinical records were available for 112 patients (68 F, mean age 37.5 years, range 15–88). In 86/112 patients, CD had been suspected because the patients had complained of gastrointestinal symptoms; in 22 patients there were no gastrointestinal symptoms and CD had been suspected because of extra-intestinal symptoms such as skin lesions suggestive of dermatitis herpetiformis (12 patients), anaemia (8), recurrent aphthous stomatitis (1) or general malaise (1). In the last four patients, CD had been suspected on the basis of familiarity; they had been on a GFD for 7.5 months (25th–75th percentile range, 3–20).

Following our investigations, a diagnosis of CD was confirmed in 51 out of 112 patients; 40 of the 51 patients had clear villous atrophy and positive endomysial antibodies. Ten out of 51 had positive endomysial antibodies and minimal intestinal lesions, and 5 of these patients were found to be affected by dermatitis herpetiformis. In the last of the 51 patients, a duodenal biopsy showed a clear villous atrophy but endomysial antibodies were negative because of common variable immunodeficiency. In these 51 patients, the median duration of gluten dietary re-introduction before performing a duodenal biopsy and serological testing was 2 months (25th–75th percentile range, 1–4). CD was confirmed in 34/86 (39.5%) patients with gastrointestinal symptoms and 17/26 (65.4%) patients without intestinal symptoms.

In the 61 patients in whom CD was excluded because of normal duodenal biopsies and negative endomysial antibodies, the median duration of gluten dietary re-introduction was 5 months (25th–75th percentile range, 2–8). Fifty-two of these patients complained of gastrointestinal symptoms and the final diagnoses were irritable bowel syndrome (22 patients), lactose malabsorption (8), infectious diarrhoea (8), food allergy (7), lymphocytic colitis (2), gastro-oesophageal reflux disease (2), small-bowel bacterial overgrowth (1), Crohn's disease (1) and chronic pancreatitis (1).

Symptoms prevalence before and after gluten had been re-introduced in the diet of both coeliac and non-coeliac patients is summarized in Table I. Although the retrospective nature of the study did not allow us to have the same clinical data for every patient, no statistically significant differences could be found. Improvement in symptoms while on a GFD had a positive predictive value for CD of 36%. Exacerbation of symptoms after dietary gluten re-introduction had a positive predictive value for CD of 27%

Table I. Prevalence of gastrointestinal symptoms and their relationship with gluten withdrawal/re-introduction in patients with and without CD.

	CD	Non-CD	χ^2 test, p
No. of patients	34	52	
Mean age	39.3 years	36.2 years	
(range)	(15–88)	(21–78)	
Diarrhoea	26/34 (76.5%)	40/52 (76.9%)	NS
Improvement while on a GFD	16/22 (72.7%)	25/38 (65.8%)	NS
Exacerbation after GR	3/6 (50.0%)	8/19 (42.1%)	NS
Weight loss	18/34 (52.9%)	26/52 (50.0%)	NS
Improvement while on a GFD	12/17 (70.6%)	12/19 (63.2%)	NS
Exacerbation after GR	1/3 (33.3%)	3/7 (42.9%)	NS
Abdominal pain	15/34 (62.5%)	26/52 (50.0%)	NS
Improvement while on a GFD	8/14 (57.1%)	18/26 (69.2%)	NS
Exacerbation after GR	2/2 (100%)	6/9 (66.7%)	NS
Upper gastrointestinal symptoms	6/34 (17.6%)	15/52 (28.9%)	NS
Improvement while on a GFD	3/6 (50.0%)	8/12 (66.7%)	NS
Exacerbation after GR	1/1 (100%)	3/8 (37.5%)	NS
Alarm symptoms*	4/34 (11.8%)	11/52 (54.2%)	NS
Improvement while on a GFD	4/4 (100%)	10/11 (90.9%)	NS
Exacerbation after GR	0/1 (0%)	5/7 (71.4%)	NS
Overall response			
Improvement while on a GFD	22/34 (64.7%)	39/52 (75.0%)	NS
Exacerbation after GR	5/7 (71.4%)	13/24 (54.2%)	NS

Abbreviations: CD = coeliac disease; GFD = gluten-free diet; GR = gluten re-introduction; NS = not statistically significant.
Clinical data were available in most patients but not in all of them.
Alarm symptoms: *fever, faecal blood, symptoms causing awakening.

Discussion

We must point out that this is a retrospective study and it therefore intrinsically carries some biases, such as the lack of standardization for both clinical records and dietary gluten re-introduction. However, these problems were equally present in both coeliac and non-coeliac patients. We thus believe that they cannot have compromised the main final conclusions. It should be noted that the dietary gluten re-introduction lasted longer in the non-coeliac group than in the coeliac group (median 5 versus 2 months). We therefore believe it is unlikely that patients in whom the diagnosis of CD was excluded were actually affected by this condition.

Food intolerance and food aversions are abnormal reactions that occur after the ingestion of food [6]. These reactions are quite common, as several studies have reported that a significant proportion of adults (20–45%) believe they suffer from food allergy, and 20–65% of patients with irritable bowel syndrome attribute their symptoms to something in food that activates an abnormal response [6–10]. However, despite the frequencies of these conditions, arriving at a correct diagnosis of food intolerance can be difficult. It has already been pointed out that elimination diets and challenge protocols reveal that patients' perceptions and physicians' diagnoses of food intolerance are invariably inaccurate [11]. Well-designed, double-blind challenge tests are thus required [12].

CD is certainly one of the most common food intolerances. Although it is characterized by specific serological and histological patterns, its clinical spectrum can overlap many gastrointestinal conditions such as irritable bowel syndrome, food allergies and lactose intolerance. Clinicians and patients themselves are aware of the high prevalence of CD [13,14] and the risks related to this condition [15,16]. However, in order either to start the therapy as soon as possible or to use it as a diagnostic test, wheat is often excluded from the diet before histological and serological investigations are performed.

A few years ago, it was shown that subjective intolerance to cereals is not specific for CD [5]. Our results confirm and expand those findings. We showed that clinical improvement after gluten withdrawal is common and is not CD specific, as it occurs in comparable percentages of patients with (64.7%) and without CD (75%). Moreover, gluten re-introduction is followed by a re-exacerbation of symptoms in both coeliac and non-coeliac patients. Therefore, modifications of symptoms following both withdrawal and re-introduction of dietary gluten do not make it possible to distinguish CD from other gastrointestinal conditions.

CD is not the only condition in which gastrointestinal symptoms improve after gluten withdrawal. Not only wheat allergy but also irritable bowel syndrome can benefit from a GFD, as wheat starch fermentation by gastrointestinal bacteria could be responsible for bloating and diarrhoea [9,17,18]. On the other hand, CD is characterized by some important features such as complications [16], associated autoimmune diseases [2] and familiarity [14] that are absent in other forms of food intolerance and irritable bowel syndrome. Therefore, whenever a diagnosis of CD is suspected, it should either be confirmed or excluded with certainty. This can only be done with duodenal biopsy and coeliac antibody testing, performed while the patient is on a gluten-containing diet.

In conclusion, we totally agree with Kaukinen et al. [5]. Since experimental or diagnostic exclusion of gluten from the diet is not a double-blind challenge test, it is useless and should be discouraged because it will only make the correct diagnosis of CD even more difficult.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Biagi F, Corazza GR. Clinical features of coeliac disease. Dig Liver Dis 2002;34:225–8.
[2] Corazza GR, Gasbarrini G. Coeliac disease in adults. Bailliere's Clin Gastroenterol 1995;9:329–50.
[3] Working Group of the United European Gastroenterology week in amsterdam 2001. When is a coeliac a coeliac? Eur J Gastroenterol Hepatol 2001;13:1–6.
[4] Working Group of the European Society for Paediatric Gastroenterology and Nutrition: revised criteria for diagnosis of celiac disease: Arch Dis Child 1990;65:909–11.
[5] Kaukinen K, Turjanmaa K, Mäki M, Partanen J, Venäläinen R, Reunala T, et al. Intolerance to cereals is not specific for coeliac disease. Scand J Gastroenterol 2000;35:942–6.
[6] Park M-I, Camilleri M. Is there a role of food allergy in irritable bowel syndrome and functional dyspepsia? A systematic review. Neurogastroenterol Motil 2000;18:595–607.
[7] Young E, Stoncham MD, Petruckevitch A, Barton J, Rona R. A population study of food intolerance. Lancet 1994;343: 1127–30.
[8] Bischoff SC, Herrmann A, Manns MP. Prevalence of adverse reactions to food in patients with gastrointestinal disease. Allergy 1996;51:811–8.
[9] Nanda R, James R, Smith H, Dudley CR, Jewell DP. Food intolerance and the irritable bowel syndrome. Gut 1989;30: 1099–104.
[10] Hischenhuber C, Crevel R, Jarry B, Mäki M, Moneret-Vautrin DA, Romano A, et al. Review article: safe amounts of gluten for patients with wheat allergy or coeliac disease. Aliment Pharmacol Ther 2006;23:559–75.
[11] Ferguson A. Definitions and diagnosis of food intolerance and food allergy: consensus and controversy. J Pediatr 1992; 121:S7–S11.
[12] Knight AK, Bahna SL. Diagnosis of food allergy. Pediatr Ann 2006;35:709–14.
[13] Corazza GR, Andreani ML, Biagi F, Corrao G, Pretolani S, Giulianelli G, et al. The smaller size of the "coeliac iceberg" in adults. Scand J Gastroenterol 1997;32:917–9.
[14] Dubé C, Rostom A, Sy R, Cranney A, Saloojee N, Garritty C, et al. The prevalence of celiac disease in an average-risk and at-risk Western European population: A systematic review. Gastroenterology 2005;128:S57–67.
[15] Corrao G, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, et al. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet 2001;358:356–61.
[16] Biagi F, Lorenzini P, Corazza GR. Literature review on the clinical relationship between ulcerative jejunoileitis, coeliac disease and enteropathy associated T cell lymphoma. Scand J Gastroenterol 2000;35:785–90.
[17] Monsbakken KW, Vandvik PO, Farup PG. The value of a general therapeutic approach in subjects with irritable bowel syndrome. Aliment Pharmacol Ther 2005;21:21–7.
[18] Niec AM, Frankum B, Talley NJ. Are adverse food reactions linked to irritable bowel syndrome? Am J Gastroenterol 1998;93:2184–90.