

Coeliac disease associated with recurrent aphthae

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SUMMARY Fifty patients presenting sequentially with a history of recurrent aphthae were investigated for evidence of nutritional deficiencies and coeliac disease. In the group, two patients were found to have coeliac disease and their recurrent aphthae cleared soon after starting a gluten free diet. This study confirms the presence of an increased prevalence of nutritional deficiency and of coeliac disease in aphthous patients. However, it is recommended that jejunal biopsy be carried out in these cases only where there is evidence of malabsorption.

Recurrent aphthae is a disorder which may have a multifactorial aetiology. Although various forms of aphthae have been described in relation to their size, distribution on the oral mucosa and duration of ulceration, these clinical criteria have not been useful in determining the aetiological factors. In an investigation of a series of patients with aphthae¹ it was noted that over 17% of all cases showed nutritional deficiency, and, of these, over half responded favourably to replacement of folic acid, vitamin B12, or iron. In an age- and sex-matched group of controls, 8.5% had evidence of similar nutritional deficiencies and, hence, in those patients with recurrent aphthae who did not respond to specific replacement therapy, there appeared to be no direct relationship between the deficiency and the oral ulcers.

In the above series reported by Wray *et al.*¹ (1975) it was found that 5% of the individuals with recurrent aphthae also had coeliac disease, this figure being considerably higher than would be expected in the general population. A subsequent study in Birmingham of 33 cases of recurrent aphthae² reported a prevalence of 24% of coeliac disease in these patients, all cases having subtotal villous atrophy. It seemed possible, therefore, that a number of patients with recurrent aphthae associated with coeliac disease were being missed when investigations of their condition were restricted to haematological examination and jejunal biopsy was carried out only when malabsorption was suspected. Accordingly, it was decided to investigate fully a group of patients presenting sequentially to the Glasgow Dental Hospital with a history of recurrent aphthae, in order to establish the prevalence of

coeliac disease in these patients regardless of haematological findings.

Antibodies directed to various food antigens have been reported in coeliac disease^{3 4} but these also appear to occur non-specifically in relation to chronic oral ulceration.⁵ However, no comparison between cases of recurrent aphthae with and without associated coeliac disease has been made and the patients were screened for antibodies to cereal and animal protein antigens.

Circulating reticulin antibodies are more common in coeliac disease⁶ and this test was conducted in order to evaluate its usefulness in screening for coeliac disease in a group of patients with recurrent aphthae.

Methods

PATIENTS

All patients diagnosed as having recurrent aphthae using previous criteria¹ were admitted to the series. The only selection of patients for this project was through their referral to the Oral Medicine Clinic by medical and dental practitioners. The study was continued until 50 patients had been fully investigated. Eighty-seven patients underwent initial screening but 37 of these were eventually discarded from the study either due to default from the Clinic or because of refusal to have a jejunal biopsy performed.

Fifty subjects completed the trial. There were 14 males and 36 females with a mean age of 30.5 years (range 13 to 60 years).

A detailed history of ulceration was obtained from each patient regarding duration, average size, precipitating factors, number per crop, mucosal distribution, time taken to heal, and time between

crops. In addition, a general medical history was taken with particular reference being paid to alimentary and dermatological disorders.

INVESTIGATIONS

Patients with a history of recurrent oral ulceration were examined and the diagnosis of aphthae made both on the grounds of a characteristic history and on clinical examination. Venous blood was removed for the various investigative procedures and then each patient underwent jejunal biopsy. No systemic treatment was administered and an aqueous 0.2% chlorhexidine mouthwash was used for symptomatic relief until the examinations were complete.

Haematology and biochemistry

The blood was examined for haemoglobin concentration, MCV, and a film evaluated. In addition the following measurements were made: corrected whole blood folate, serum vitamin B12, serum iron and total iron binding capacity, total serum proteins and electrophoresis, albumin, calcium, and phosphate. Where a result was either abnormal or in the borderline region, the test was repeated.

Gluten antibodies

Aqueous extracts of wheat flour, oatmeal, and gluten were prepared and a microgel diffusion test^{7 8} carried out on sera.

Animal protein antibodies

Circulating antibodies were detected using precipitin tests and by passive haemagglutination.⁵

Reticulin antibodies

Sera were examined for the presence of antibodies (IgA) to reticulin. Using an immunofluorescent technique, titres of up to 1:1000 were found to be positive for rabbit kidney reticulin fibres in individuals with circulating reticulin antibodies. For the present investigation all sera were examined initially at a dilution of 1:16.

Jejunal biopsy

The jejunal biopsies were obtained using a Crosby-Kugler capsule attached to polyvinyl tubing and passed into the jejunum under radiological screening until approximately 10 cm distal to the ligament of Treitz.⁹ The biopsies obtained were divided into two portions, one of which was immediately frozen and later analysed for disaccharidase activity (lactase, sucrase, maltase), using the method of Dahlquist.¹⁰ The other portion was histologically assessed without knowledge of the clinical or haematological status of the patients. Each biopsy was examined under the dissecting microscope as well as being

prepared for standard histological assessment. The histological assessment included examination for significant alteration in main mucosal measurements (villus height, crypt height/villus ratio) and infiltrate.¹¹ Significant atrophy of the mucosa was considered to be present if the villus height was less than 300 μ and the crypt/villus ratio was greater than 0.6. Subjective assessment of lymphocyte content of the lamina propria and epithelial surface was also made.

Results

Of the 50 patients being fully investigated two females were eventually diagnosed as having coeliac disease. One had a six-month history of recurrent oral ulceration and the other a six-year history: their ages were 48 years and 26 years respectively. The ulcers were characteristic of minor aphthae with an average size of 5 mm and typical mucosal distribution. Neither patient gave a history of dermatological disease and no cutaneous or other mucosal lesions were found. One gave a history of chronic constipation together with the production of foul-smelling stools which tended to be difficult to flush away. The final diagnosis was confirmed in these two patients by their clinical response to a gluten free diet together with replacement therapy. Repeat jejunal biopsies were performed four months after starting on a gluten free diet and the histology showed a return to normal.

The number of patients out of the 48 who had abnormal results is shown in Table 1 and the results from the two patients with coeliac disease are listed for comparison in Table 2. Of the six abnormal

Table 1 *Abnormal haematological and biochemical results in 48 patients with recurrent aphthae*

Investigation	Number	Normal values
Hb	5	Males > 12.5g/dl; females > 12.0g/dl
MCV	6	80-100 fl
Film	5	—
Whole blood folate	6	> 100 ng/ml
Serum vitamin B12	1	> 240 pg/ml
Iron saturation	9	> 16%

Table 2 *Haematological and biochemical values of two patients with recurrent aphthae and coeliac disease*

Test	Patient A	Patient B
Hb	11.2	11.1
MCV	104	97
Film	Macrocytic	Normal
Whole blood folate	64	58
Serum vitamin B12	380	430
Iron saturation (%)	52	7

MCV values in the non-coeliac patients, three were associated with iron deficiency and one with folate deficiency. Two patients had a combined iron and folate deficiency; therefore the total number with a deficiency was 14. Of these 14 patients with a deficiency, only five had an abnormal haemoglobin or MCV. The haematological values of the 37 patients not biopsied were comparable with the 50 and did not show any significant difference.

Antibodies to an aqueous extract of wheat flour, oatmeal, or gluten were not detected in any of the patients including the two cases with coeliac disease.

Table 3 Food antibodies in 48 patients with recurrent aphthae (with two coeliac disease excluded) and two patients with coeliac disease

	Patients	
	48	2
Cereal antigens (precipitin)	0	0
Cow's milk (precipitin)	2	0
Calf's serum (precipitin)	1	0
Chicken's serum (precipitin)	0	0
Cow's milk antibody score (passive haemagglutination tests)		
0	35	0
1-4	8	2
5-15	5	0
16+	0	0

The results of the tests for antibodies to animal protein are shown in Table 3. In the two patients with coeliac disease, neither had antibodies using the precipitin test but one had a milk antibody score of 4 and the other a score of 1.

Antibodies to reticulín were demonstrated to be present in one of the 50 patients under investigation, but this individual did not have coeliac disease and had no other haematological abnormality.

The two patients were diagnosed as having coeliac disease from the finding of subtotal villous atrophy in the jejunal biopsy. The remaining 48 were normal and showed no evidence even of partial involvement.

Sufficient jejunal mucosa to carry out enzyme studies was obtained from 94% of the 50 patients. Of these, 24% had a low value for one or more of the disaccharidases. Unfortunately, enzyme studies were carried out in only one of the two patients with coeliac disease and this had a low value for sucrase.

PROGRESS

The two patients diagnosed as having coeliac disease were placed on a gluten free diet and their nutritional deficiencies rectified by dietary supplements: folic acid was given to each and ferrous sulphate to the one who also had iron deficiency. In both cases there was a marked improvement with the oral ulceration clearing within one month. These

patients have now been followed for two years and neither has experienced any further aphthae.

Discussion

In this series of 50 'unselected' patients with recurrent aphthae, two (4%) were diagnosed as having coeliac disease. This incidence is in agreement with our previous study on patients with recurrent aphthae¹ and is very much lower than the Birmingham series.² The reason for this discrepancy is not apparent: the source of patients was supposed to be comparable and the diagnosis of recurrent aphthae made using the same clinical criteria.

The two patients with coeliac disease had recurrent aphthae of the minor pattern and no obvious difference existed in the several physical properties of their oral ulcers as compared with the remainder of the group. Neither had any other clinical evidence—for example, glossitis or angular cheilitis—to support the diagnosis of a nutritional deficiency, although one did admit to having alimentary symptoms which were suggestive of malabsorption.

Biochemical evidence of a nutritional deficiency was found in 28% of the patients but this was not always reflected in the haemoglobin, MCV, or blood film; 10% of the patients had an abnormal haematological result. Both cases of coeliac disease had clear evidence of folate deficiency and this was reflected in a reduced haemoglobin. However, only one showed an abnormal MCV and blood film, whereas the second patient, who also had iron deficiency, had a normal MCV and film. Other biochemical tests used to detect malabsorption include serum albumin, calcium, and inorganic phosphate but these values were within normal limits for the two coeliac patients.

Patients with coeliac disease often have circulating antibodies to wheat or gluten extracts^{3,7} as well as to several other dietary antigens.¹²⁻¹⁴ Coeliac patients are able to tolerate foods other than those containing gluten and the current consensus of opinion is that these serum antibodies are related to the increased permeability to macromolecules of the inflamed intestinal mucosa.^{1,5,16} This is supported by the fact that patients with oral ulceration from various causes may have a greater incidence of food antibodies.⁵ Testing for antibodies to food antigens appears to provide no useful information in patients with recurrent aphthae and does not identify patients with coeliac disease. Further, when this larger group of patients with recurrent aphthae was examined the incidence of avian antibodies was no greater than that found in controls and the difference in CMA score not as striking.

Reticulin antibodies are found more commonly

in coeliac disease patients, although we failed to demonstrate these in two patients with coeliac disease in the present study and obtained a positive result for one other patient who was otherwise normal. Therefore it would seem not to be a particularly useful test in the screening of aphthous patients for coeliac disease.

In conclusion, it would appear that the prevalence of coeliac disease is higher in patients with recurrent aphthae than in the general population but this is not nearly as common in this study as previous work indicated. These findings do not support the necessity of routine jejunal biopsies in all patients with aphthae.

In the present series, both patients with coeliac disease were found to have folate deficiency, and the prevalence of folate deficiency in aphthous patients was previously documented.^{1, 2, 17}

Nutritional deficiencies not uncommonly exist without changes occurring in the level of haemoglobin, the MCV, or the blood film. Accordingly, it is our opinion that patients presenting with recurrent aphthae should be screened for folate, vitamin B12, and iron deficiency at their initial presentation. Further, if a patient with recurrent aphthae is found to have a depressed whole blood folate then it is reasonable to perform a jejunal biopsy: in the present series two of the eight patients with a low folate concentration were found to have coeliac disease.

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