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CLINICAL REPORT

Frequency and Prognostic Value of IgA and IgG Endomysial Antibodies in Recurrent Aphthous Stomatitis

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Recurrent aphthous stomatitis is a common disease of the oral mucous membranes. Currently a hypothesis is being discussed that it might be pathogenetically related to coeliac disease. We evaluated the frequency of coeliac disease anti-endomysial (or anti-transglutaminase) antibodies in patients with recurrent aphthous stomatitis. Blood samples from 42 patients were evaluated and 2/42 (4.7%) were IgA- and IgG-endomysial antibody-positive. None of the 42 persons in the control group had antibodies, which was not statistically different from the patient group. The two antibody-positive patients had episodes of mild gastrointestinal symptoms only, but histopathology of duodenal mucous membranes confirmed coeliac disease. All symptoms related to aphthous stomatitis responded well to a gluten-free diet. We conclude that every patient with recurrent aphthous stomatitis should be asked about a history of gastrointestinal complaints and screened for markers of coeliac disease, since recurrent aphthous stomatitis may in some cases respond to a gluten-free diet. ***Key words: aphthae; aphthous ulcers; canker sores; oral ulcers; gluten enteropathy; sprue.***

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Recurrent aphthous stomatitis (RAS) is an inflammatory condition characterized by painful recurrent, single or multiple ulcerations of the oral mucosa. It is estimated that up to 20% of individuals have been afflicted at least once with aphthous ulcers and about 5–20% have had an episode of RAS (1). The disease occurs in men and women of all ages, races and in all geographic regions.

Although RAS is a common disease of oral mucous membranes, its aetiology and pathogenesis remains unknown (2, 3). It was shown that genetic, immunological and microbial factors may play a role in the pathogenesis. Attacks may be precipitated by local trauma, stress, food intake, drugs, hormonal changes or vitamin and trace element deficiencies (3). However, no principal cause has been discovered.

RAS may be pathogenetically related to coeliac disease and the question is whether treatment of coeliac disease may induce an improvement in RAS (4–6).

Coeliac disease is a common disorder of the small intestine mediated by immunological processes initiated by exposure to dietary gluten in genetically susceptible individuals. It is characterized by a variety of clinical presentations, which usually incorporate typical malabsorption syndrome and several non-classical symptoms, including loose skin folds, peripheral oedema, ecchymoses, hyperkeratosis, dermatitis herpetiformis, cheilosis or glossitis. However, many cases of coeliac disease remain clinically silent and undiagnosed (7, 8).

In order to aid the diagnosis of coeliac disease, a specific serological test for the presence of endomysial antibody (EMA) has been developed.

Available tests for EMA detect IgA auto-antibodies (IgA EMA) directed against the endomysium in monkey oesophagus by indirect immunofluorescence or by enzyme-linked immunosorbent assay (ELISA). This method is considered to have a 99–100% specificity (9–12) and approximately 94% sensitivity. A disadvantage of this test is its limited value in patients with IgA deficiency, which is found in 2–3% patients with coeliac disease (13). For this reason, another test has been established, the IgG EMA, where the auto-antigen is recognizing anti-endomysial IgG antibodies (14). In doubtful cases IgG class anti-EMA may be evaluated either by indirect immunofluorescence or by ELISA. This test is believed to have lower specificity, but higher sensitivity (15).

In a study by West et al. (16) the prevalence of anti-EMA in the general population is 1.2%.

The aim of this study was to evaluate the prevalence of coeliac disease markers IgA EMA and IgG EMA in patients with RAS and to assess whether patients with confirmed coeliac disease showed any effect of a gluten-free diet.

MATERIALS AND METHODS

A group of 42 consecutively referred adult patients (19 women and 23 men) with RAS of at least 1-year duration were included in the study. The age range in the patient group was 18–69 years (mean 36 years). The control group consisted of 42 consecutively referred patients of the dermatology out-patient office in the Dermatology Department of Warsaw Medical School, with no history of aphthous stomatitis or any other skin condition

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related to coeliac disease. Also, none of the patients or control persons had a diagnosis of coeliac disease.

All patients' sera were evaluated for the presence of IgA EMA and IgG EMA by means of indirect immunofluorescence, as first described by Chorzelski et al. (17).

In all patients a detailed gastrointestinal medical history was taken, and in patients positive for EMA histopathological evaluation of duodenal mucous membrane biopsy was performed.

Mann-Whitney U-test was used for statistical analysis, and the level of significance was set at $p<0.05$.

RESULTS

Both IgA EMA and IgG EMA were detected in 2 (4.7%) out of 42 patients. No patient was positive for only one EMA isotype, IgA or IgG. None of the control individuals was positive for either IgA EMA or IgG EMA (0%). The difference was not statistically significant.

One patient positive for IgA EMA and IgG EMA was a 33-year-old woman, referred to our outpatient clinic with a 2-year history of pronounced aphthous stomatitis. A detailed medical history revealed that the patient had minor abdominal discomfort and occasional diarrhoea. Laboratory investigations showed decreased serum iron levels and mild anaemia. Immunopathological studies revealed the presence of IgA EMA antibodies at a titre of 160 and IgG EMA antibodies at a titre of 40. Histopathology of macroscopically unchanged mucous membrane of the duodenum showed elements characteristic of coeliac disease, including flattening, broadening and coalescence of villi and mild infiltration with lymphocytes, plasma cells and eosinophils. The patient was given a gluten-free diet. Within the next 6 months the patient became free of gastrointestinal symptoms and the oral lesions healed almost completely.

The other patient, a 58-year-old woman, was positive for IgA EMA and IgG EMA, at titres of 320 and 80, respectively. She had a 7-year history of severe, continuous RAS and no gastrointestinal complaints other than occasional diarrhoea. Also in this patient histopathology of duodenal biopsy showed flattening and broadening of villi, characteristic of coeliac disease. All basic laboratory tests, including blood count and iron plasma levels, were within the normal range. In this patient introduction of a gluten-free diet produced significant improvement within 3 months and total clearance of all lesions of the oral mucosa within 6 months. The patient is now continuing her gluten-free diet and she has now been free of any lesions for several months.

DISCUSSION

Although a first report of aphthous oral ulcers in patients with coeliac disease was published by Ferguson et al. (18) several years ago, just recently the question has been raised by several authors as to whether RAS might be pathogenetically related to coeliac disease and whether treatment of coeliac disease may induce improvement in RAS.

A study by de Freitas et al. (19) has shown that a significantly increased percentage of patients with coeliac disease suffer from aphthous stomatitis. A detailed analysis performed by these authors revealed that up to 31% of patients with coeliac disease show clinical manifestations of aphthous stomatitis. The estimate of other authors demonstrates that the prevalence of RAS in patients with coeliac disease is between 10–18% (3). In a recent paper, Aydemir et al. (5) describe two cases of coexistence of RAS and histopathologically confirmed coeliac disease and formulate the hypothesis of a pathogenetic relationship between these two diseases. Currently, some authors consider RAS to be a clinical manifestation of coeliac disease (3, 4)

On the other hand, several authors doubt the relationship between coeliac disease and RAS. Sedghizadeh et al. (20) could not confirm increased prevalence of aphthous stomatitis in patients with coeliac disease. Nowak et al. (6) focused on patients with RAS and evaluated their sera for presence of IgA EMA. In an investigation, which included 20 patients with RAS, only one patient was IgA EMA positive. The patient, however, was not evaluated for coeliac disease. Similar results were obtained in a Singapore study (21).

In our study the frequency of IgA EMA, characteristic for coeliac disease, was evaluated in 42 patients with RAS. Two out of 42 patients (4.7%) and none in the healthy control group were IgA EMA and IgG EMA positive. In both these patients coeliac disease was confirmed by histopathology, even though the patients were free of typical clinical symptoms of this disorder. In both patients all symptoms related to aphthous stomatitis responded well to a gluten-free diet, what may confirm a possible relationship between coeliac disease and RAS in these patients.

We conclude from the results of this study that every patient with RAS should be asked specifically about gastrointestinal complaints and screened for IgA EMA in order not to miss possible intestinal disease. Patients positive for IgA EMA may respond to a gluten-free diet only, with no additional pharmacotherapy.

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