

Intestinal permeability in irritable bowel syndrome. Effect of diet and sodium cromoglycate administration

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We studied 14 patients with irritable bowel syndrome for the presence of increased intestinal permeability to food antigens and their responses to diet with and without disodium cromoglycate. After a standardized oral challenge with cow milk, serum β -lactoglobulin was increased above control values in three patients.

This finding did not correlate with response to hypoallergenic diet or treatment with disodium cromoglycate for 3 weeks. However over 50% of patients improved after diet with and without DSCG (2/5 on diet only and 5/7 with disodium cromoglycate of 12 evaluable cases). Since only two patients had elevated serum IgE levels, our results suggest that intolerance rather than hypersensitivity to foods may play a role in this disease. The tests we used to identify immunologic mechanisms could not predict which patients would do better on the diet and/or the drug.

INTRODUCTION

Irritable bowel syndrome (IBS) represents a functional intestinal disorder that is very common, and is responsible for frequent absence from work.^{1,2} The disorder is characterized by abdominal pain or discomfort, accompanied by alternating of diarrhea and constipation, and flatulence. Most investigations of IBS yield normal or equivocal results. There is no evidence of organic disease. For this reason psychologic factors are thought to play a major role in the pathogenesis of IBS. Drugs commonly used in this disorder, such as antispasmodics and tranquilizers, give unsatisfactory results and no long-term relief in these patients.

Recently, several authors have suggested that specific food intolerance or hypersensitivity may play a role at least in a proportion of IBS cases.³⁻⁵ Their reports have attracted great interest because of the possibility of simple therapeutic measures such as elimination diets^{4,5} or the use of the antiinflammatory

agent, cromolyn sodium (DSCG) in the effective control of symptoms in this refractory condition.⁶

We investigated the response to diet with and without DSCG in 14 patients with classical symptoms of IBS, and correlated clinical observations with measures of intestinal permeability.

PATIENTS AND METHODS

Patients were selected for the presence of the following symptoms for over 6 months: (1) abdominal pain without organic cause; (2) periodic diarrhea with alternate constipation; and (3) meteorism, flatulence, or abdominal tension. Eleven females and three males were studied, aged 17 to 59 years. One patient (no 4) also suffered from arthralgia, without serologic or radiologic evidence of arthritis. All were subjected to 3 weeks of diet, including only the following foods: whole rice and flour, fresh salad, carrots, potatoes, all types of meat excluding chicken and veal, apples, pears, olive oil, salt, spring water, tea, sugar. Seven received in addition to the diet 750 mg daily of DSCG (250 mg three times daily). To evaluate the effect of 3 weeks of treatment, patients recorded daily the following parameters: the abdominal pain, number of bowel movements, meteorism or

flatulence, and subjective assessment of overall improvement on an analogue scale. At the end of the trial, an evaluation was made by a gastroenterologist.

All patients were subjected to oral challenge after overnight fasting, with 10 mL/kg body weight of fresh cow milk at the beginning of the study. Blood samples were collected before, two, and four hours after milk intake to evaluate intestinal absorption of macromolecules. Time points of sampling were chosen in order to minimize discomfort to patients, and also because two hours has been shown to represent the peak of circulating β -lactoglobulin in patients with abnormal permeability. At this time (two hours) the majority of normal subjects show very little absorption, which may be higher after 30 to 60 minutes from challenge.⁷⁻⁹ A second challenge was performed after 3 weeks of treatment in the seven patients receiving DSCG in addition to the diet.

Circulating immunoreactive β -lactoglobulin (BLG) was measured in patients' sera by a specific and sensitive immunoradiometric assay.⁷ Maximal BLG concentration measured in either 2-hour or 4-hour samples was assumed to indicate intestinal permeability to macromol-

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ecules during each challenge. Ten normal controls were chosen among the staff and subjected to the same challenge. Their results are indicated as normal values.

The following proteins were also measured in the first (prediet, prechallenge) serum sample: antibodies to BLG,¹⁰ total serum IgE (Phadezym PRIST, Pharmacia, Uppsala), and IgG anti-IgE autoantibodies.¹¹ IgG antibodies to BLG were also measured in the first sample of the second challenge in the seven cases tested. Circulating immune complexes (CIC) containing IgG, IgA, and IgM were also investigated in sequential serum samples during the challenges by indirect immunofluorescence using the Raji cell method.¹²

RESULTS

Clinical Response to Diet

Twelve patients were evaluated after 3 weeks of diet. Of these, seven received also DSCG. Two out of five on the diet, and five out of seven on DSCG and diet showed a clear reduction of symptoms. Five other patients experienced no change of symptoms during the diet period, two of them being on DSCG (see Table 1).

Intestinal Permeability Measurements

No adverse reaction to cow milk was observed in any case, so BLG detection in serum after milk challenge was assumed as a measure of intestinal permeability to macromolecules. Before beginning the diet, levels of circulating BLG were abnormally increased in 3/14 cases (normal values < 0.3 ng/mL, Fig. 1). Two of these did not respond to diet and one was not evaluable for discontinuation of the diet. So peak levels of circulating immunoreactive BLG were within the controls' range in 11/14 patients. In the seven patients who underwent a period of diet including DSCG administration, BLG absorption values were more homogeneous and their

means lower, although not significantly lower, than the average levels of the total group with IBS (0.13 ± 0.17 ng/mL). One of the three cases with increased permeability was included in this sample.

All patients showed reduced intestinal permeability during the posttreatment challenge (Fig. 2a)

Table 1. Clinical Features of Patients with Irritable Bowel Syndrome

Patient No	Sex	Age, yr	DSCG	Response to Diet
1	F	25	no	no improvement
2	F	35	no	no improvement
3	M	40	no	not evaluable
4	F	39	no	no improvement
5	F	22	no	improved
6	M	41	no	not evaluable
7	F	35	no	improved
8*	F	56	yes	improved
9	F	17	yes	improved
10	F	34	yes	improved
11	F	20	yes	no improvement
12	F	41	yes	improved
13	F	59	yes	improved
14	M	49	yes	no improvement

* Patient no 8 also improved on diet only.

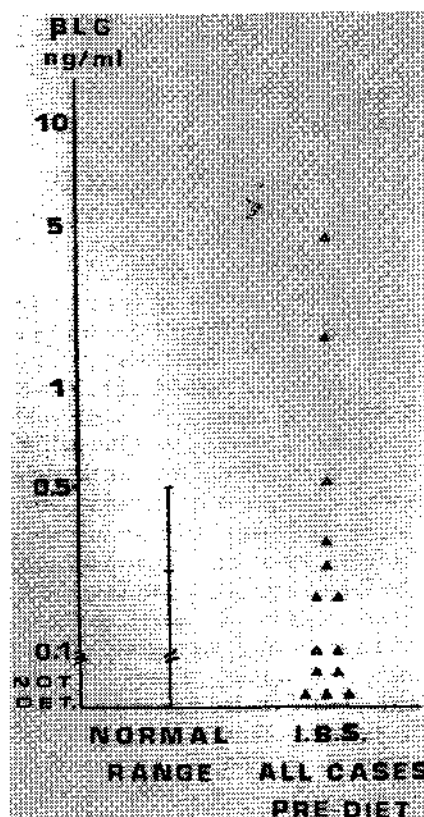


Figure 1. Immunoreactive β -lactoglobulin detected in postchallenge sera of untreated patients with IBS and normal controls.

with mean values decreasing to 0.03 ± 0.05 ng/mL ($P > .1$, not significant). Since the cut-off value for BLG detection is 0.1 ng/mL, this means that BLG was measurable only in two out of seven cases, compared with four before the diet.

Other Immunologic Variables

IgE levels were within the normal range (below 100 IU/mL) in all but two cases tested. Specific IgE to cow milk was negative by RAST in 7/7 sera from patients who underwent the diet and DSCG trial. IgG antibodies to BLG were only slightly increased in eight patients' sera versus controls (mean 46.4 ± 53.6 ng/mL equivalents of IgG). After diet (excluding dairy products) and DSCG administration, a nonsignificant decrease of IgG antibodies to BLG was detected (Fig. 2b).

Circulating immune complexes after challenge with cow milk were found in 9/13 patients' sera studied before diet. These were of the IgG class in all but one case. Such IgG-containing CICs were still present, although at lower titers, in the seven patients challenged a second time after diet and DSCG for 3 weeks (data not shown).

IgG autoantibodies to IgE were not found in ten cases whose prechallenge sera were tested. In one additional patient (no. 2, also showing high intestinal permeability and no response to diet) we detected this autoanti-IgE antibody at low levels. None of the immunologic variables investigated in this study correlated

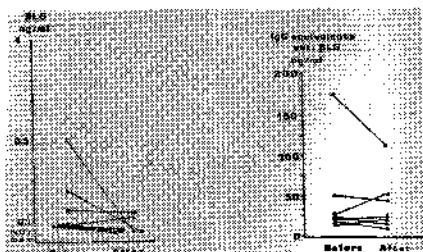


Figure 2. Maximal levels of β -lactoglobulin (left panel) and IgG antibodies to β -lactoglobulin (right panel) in sera of patients with IBS before and after 3 weeks of diet and DSCG.

with clinical outcome of diet or diet plus DSCG administration, so they were not predictive of the response to the treatment.

DISCUSSION

We studied the intestinal permeability to a macromolecule (BLG) after oral challenge with cow milk in 14 patients with IBS, and found that 3/14 (21%) had increased levels of immunoreactive BLG in their sera. This finding shows increased passage of antigenic material, which has been demonstrated in other conditions such as atopic eczema, food allergy, IgA deficiency, and parasitic infections of the gut.^{13,14} The use of two time points for sampling does not prevent higher absorption from occurring earlier or later. This seems to be a remote possibility since even in food anaphylaxis peak levels are observed after two hours, and generally very little immunoreactive food proteins can be demonstrated after four hours.^{8,9,13} Seven of 12 patients who underwent 3 weeks of oligoallergenic diet with and without DSCG showed a >50% improvement in their symptoms. Measurement of intestinal absorption, CIC formation, and IgE and IgG antibodies to cow milk proteins could not distinguish between those who received clinical benefit from the diet and those whose symptoms remained unchanged. None of our cases, except perhaps one, was atopic by conventional tests and none was allergic to cow milk. Our series therefore seems to be at variance with others reported with respect to atopy, which was present in 20% of IBS,¹⁵ up to 50%,⁴ 60%,⁵ and 74%.⁶ Despite the differences in the incidence of atopy in the cases selected, confirmation of food hypersensitivity (or intolerance) varied in these studies. Alun Jones reported 67% of 21 patients being symptom-free after 1 week of strict diet, although 89% of them were nonatopic,^{3,16} whereas Bentley et al¹⁵ confirmed food hypersensitivity only in three atopic IBS patients out

of 19 who were investigated. Petitpierre et al⁴ reported that 14/24 IBS patients responded to a diet, although objective confirmation of food intolerance by double-blind challenge could be obtained only in seven. In his study, ten of the responders also suffered from classical atopic symptoms, but still 30% (four out of 12) of nonatopic IBS patients showed improvement after 3 weeks of diet.

In our study we observed a response to diet in 50% of the cases, none of them being atopic, and up to 70% in seven patients treated with diet and DSCG. The diet excluded cow milk and dairy products, although we found no evidence of hypersensitivity to milk in our series. Measurement therefore of immunoreactive BLG in sera was assumed to represent a marker of intestinal absorption of antigen. The results showed a slight reduction of intestinal permeability after 3 weeks of diet and DSCG, and also of IgG antibody response to BLG. But these changes were detected also in the two patients not responding to treatment, perhaps indicating that this represents a phenomenon of decreased antigenic load leading to decreased production of inflammatory mediators. It is in fact controversial whether DSCG is effective only in IgE-mediated hypersensitivity,^{13,17} since many authors have reported beneficial effects in treating additive intolerances and pseudoallergic reactions.^{18,19} In IBS it has been postulated that a proportion of patients suffer from IgE-mediated food allergy^{4,6} but others react to foods and therefore improve with diet because of other mechanisms. Intestinal infections and food intolerance seem to play a major role in nonatopic IBS patients. This may be reinforced by the findings of Alun Jones et al,³ who reported an increase of rectal PGE₂ in relation to positive food challenges. Because they found no evidence of IgE-mediated hypersensitivity in their patients, they explain their results with reference to

pseudoallergic mechanisms of intolerance to foods.

Our findings confirm that oligoantigenic diet and DSCG are beneficial in a substantial proportion of patients with IBS. This treatment also decreases intestinal permeability, although this was previously abnormal in only 20% of our cases. This, as well as other variables, does not seem helpful in the selection of patients who will benefit from dietary manipulations.

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