Intestinal permeability in Behçet's syndrome

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Abstract

Objective—To measure the intestinal permeability in patients with Behçet's syndrome (BS) and to compare the results with those obtained from healthy and diseased controls.

Method—The study group comprised 34 patients with BS without known gastro-intestinal disease. Ten patients with ankylosing spondylitis (AS), 6 with inflammatory bowel diseases (IBD), 17 with systemic lupus erythematosus (SLE), and 15 healthy subjects (HC) constituted the controls. All patients received 100 µCi (3.7 MBq) of chromium-51 EDTA (⁵¹Cr-EDTA) as a radioactive tracer after a 72 hour abstinence from all drugs. The percentage of the isotope excreted in a 24 hour urinary specimen was the measure of permeability. **Results**—The percentage (SD) rate of excretion of ⁵¹Cr-EDTA was 4.6 (2.6) in BS, 6 (2.4) in AS, 5.2 (1.9) in IBD, 5.56 (1.78) in SLE, and 2.3 (1) in healthy controls. (Analysis of variance: $f=6.4$, $p=0.0002$. BS *v* HC, AS *v* HC, SLE *v* HC significant.)

Conclusion—The intestinal permeability in BS was significantly more than that seen among the healthy controls. Similar results in all the diseased controls cast doubt on its specificity.

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IBD, AS, systemic lupus erythematosus (SLE), and in healthy hospital staff. Chromium-51 labelled ethylenediaminetetraacetic acid (⁵¹Cr-EDTA) was used as the radioactive tracer.

Patients and methods

The study was approved by the hospital ethics committee and the investigational nature of the study was explained to all participants.

Thirty four patients with BS who regularly attended the outpatient department of the BS research centre of Cerrahpaşa Medical School, Istanbul, Turkey were studied together with the controls comprising 10 patients with AS, six with IBD (four with ulcerative colitis and two with Crohn's disease), 17 with SLE, and 15 healthy people (HC). They were recruited to the study during their routine visits to the clinic from among the patients who had not used any non-steroidal anti-inflammatory drugs (NSAIDs) during the preceding three months.

A chart review of all the patients and controls was performed to determine their clinical findings and the drugs used.

Table 1 shows the clinical characteristics of the patients with BS. None of the patients with BS had any signs or symptoms that could be attributed to GI disease.

The patients with SLE were chosen from among those who did not have renal disease. Furthermore, they did not have any symptoms or signs, such as recent weight loss or diarrhoea, that could be attributed to malabsorption.

All patients received 100 µCi (3.7 MBq) of ⁵¹Cr-EDTA measured by a Capintec Radioisotope Calibrator (CRC-120) in 200 ml of water, after an overnight fast following a 72 hour abstinence from all drugs, such as salazopyrine, colchicine, azathioprine, and cyclosporin A. Twenty four hour urinary specimens were collected and the amount of radioactivity excreted in 1 ml of urine was counted in a Packard Cobra II Auto-gamma counting system. The permeability was the percentage of the absorbed pharmaceutical drug found in the urine and was calculated according to the formula: % absorption = (radioactivity of 1 ml of urine × urinary volume × 100)/(standard radioactivity × 1000).

Table 1 Clinical characteristics of the patients with Behçet's syndrome

	No (%)
Oral aphthae	34 (100)
Genital ulcers	27 (79)
Osteofolliculitis	23 (68)
Erythema nodosum	22 (65)
Arthritis	12 (35)
Eye disease	18 (53)
Neurological disease	3 (9)
Thrombophlebitis	3 (9)
Arterial disease	2 (6)
Epididymitis	1 (3)

The lumen of the gut has a reservoir of micro-organisms and their toxic products. An important function of the gut is to serve as a barrier that limits contamination by these agents. Several diseases disrupt the continuity of this barrier and result in increased rates of permeability. Inflammatory bowel disease (IBD)¹ and ankylosing spondylitis (AS)² are examples. In the clinical setting, intestinal permeability is determined by quantifying the urinary excretion of various water soluble probes that are not absorbed from the gut under physiological conditions.

Behçet's syndrome (BS) is a vasculitis characterised by a heightened state of inflammation but the mechanisms underlying this inflammatory state are largely unknown. Gastrointestinal (GI) disease in BS shows geographical variation. It is reported frequently in the Far East, whereas it is quite rare in Turkey.³ Ileocaecal ulcerations that mimic IBD constitute the hallmark of GI disease. Subclinical GI disease may conceivably occur in BS in the absence of overt presentation, similar to the situation seen in many patients with AS.⁴ Furthermore, changes in intestinal permeability may have pathophysiological consequences in BS.

Intestinal permeability was studied in a group of patients with BS and in controls with

Table 2 Demographic characteristics of the patients and the percentages of ^{51}Cr -EDTA excreted

Groups*	Sex and age (years (SD))	Excretion (% (SD))
BS (n=34)	20M, 14F (37 (10))	4.6 (2.6)
AS (n=10)	8M, 2F (33 (13))	6 (2.4)
IBD (n=6)	2M, 4F (40 (18))	5.2 (1.9)
SLE (n=17)	9F (29 (11))	5.56 (1.78)
HC (n=15)	9M, 6F (35 (10))	2.3 (1)

Analysis of variance: $f=6.4$, $p=0.0002$. The significance disappears once the healthy group is removed.

*BS = Behçet's syndrome; AS = ankylosing spondylitis; IBD = inflammatory bowel disease; SLE = systemic lupus erythematosus; HC = healthy controls.

Any adverse events that might have been related to the ingestion of ^{51}Cr -EDTA were noted. To evaluate reproducibility the study was repeated after one year in 10 of the patients with BS initially recruited.

Glomerular filtration rates were determined in 24 patients with BS, six with AS, six with IBD, 14 with SLE, and in eight HC.

Analysis of variance was used to compare the means of the percentages of radioactivity excreted in each group and Student's t test was used to evaluate the changes seen in the 10 patients with BS who underwent the procedure for a second time.

Results

Table 2 shows the demographic characteristics of the patients and the percentages of ^{51}Cr -EDTA excreted.

Permeability was significantly increased in patients with BS compared with healthy controls. There was no significant difference, however, in the excretion rates of ^{51}Cr -EDTA between BS, AS, IBD, and SLE.

There were also no significant changes in the permeability rates among the 10 patients with BS studied twice, one year apart (4.77 (1.3) v 4.21 (2.03), $p=0.36$).

None of the patients in the study and control groups had renal insufficiency judged from the glomerular filtration rates (maximum serum creatinine of 12 mg/l) in the chart reviews, and there were no adverse events that could be related to the use of ^{51}Cr -EDTA.

Discussion

^{51}Cr -EDTA is a small molecular weight solute that has consistently been used in intestinal permeability studies.⁵ It is a cheap compound with low radioactivity and has no adverse effects.⁶ Repeat measurements in 10 of our patients with BS suggest that it is a probe with reproducible results.

Two different probes with differing molecular weights⁷ have also been used in simultaneous studies with the aim of limiting the confounding effects related to before and after mucosal factors, such as gastric emptying time, intestinal blood flow, renal function, and bacterial degradation.⁵¹Cr alone, however, has an acceptable sensitivity in measuring intestinal permeability, though it is not as specific as using two simultaneous probes.⁸

It may be argued that a 72 hour wash out period was insufficient to exclude drug effects on intestinal permeability. Ethical concerns,

however, prevented us from using a longer period of abstinence. Another factor to be emphasised is that none of our patients with BS had been using an NSAID during the previous three months, which is important given that NSAIDs have consistently been associated with an increase in intestinal permeability.⁹

We could find only one previous study that had looked at intestinal permeability in SLE.¹⁰ No changes from healthy controls were found. In addition, a review on SLE has cautioned that occasional increases are related to protein losing enteropathy.¹¹ The absence of clinical signs of protein losing enteropathy among our patients with SLE suggests that other factors may be operative in the increased permeability we noted.

Similarly, although the increase in intestinal permeability we found in BS may have been the direct consequence of GI disease, we think that the uniform absence of GI symptoms in our patients with BS makes this hypothesis rather unlikely. We could not justify obtaining an intestinal biopsy sample from our patients because all of them were asymptomatic.

Factors associated with inflammation, such as oxidant stress,¹² cellular hypoxia,¹³ the generation of nitric oxide,¹⁴ and exposure to various cytokines,¹⁵ have been related to increased intestinal permeability. The increase in intestinal permeability we noted in BS, together with the diseased controls, including SLE, suggests that our finding in BS was probably secondary to inflammation.

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