Increased Intestinal Permeability in Atopic Eczema


Department of Immunology, Institute of Child Health, London, and the Hospital for Sick Children, London, U.K.

We have investigated gastrointestinal permeability in children with atopic eczema by measuring the relative urinary excretion rates of the inert di- and monosaccharides lactulose and rhamnose following their oral administration. The median lactulose/rhamnose ratio was greater in 26 children with atopic eczema than in a control group of 29 children which included both healthy individuals and others with various noneczematous dermatoses. This increased permeability may be a primary abnormality of the gut or may reflect intestinal mucosal damage caused by local hypersensitivity reactions to food antigens. J Invest Dermatol 86:101-104, 1986

SUBJECTS

Twenty-six children of various races, with a clinical diagnosis of atopic eczema, were studied (8 girls, 18 boys; age range 1.3-16.2 years, mean 5.8 years). All were receiving standard topical treatment, which in many cases included mild corticosteroid applications. Several were receiving oral antihistamines at night and some were avoiding certain foods as part of their treatment.

Two control groups were used: 23 healthy children, mostly relatives and friends of members of the department (10 boys, 13 girls; age range 0.5-14 years, mean 8.2 years) and 6 children with generalized noneczematous skin disorders comprising 2 patients with recessive dystrophic epidermolysis bullosa, 1 with bullous ichthyosiform erythroderma, and 3 with psoriasis (3 boys, 3 girls; age range 5-14 years, mean 7.3 years). None of these control children had eczema, asthma, or hay fever and they were not skin tested.

Informed consent was obtained from all parents, and approval for the study was obtained from the Hospital's Standing Committee on Ethical Practice.

METHODS

On the morning following an overnight fast of at least 6 h and after voiding and discarding overnight urine, the subjects were given l-rhamnose (0.02 g/kg body weight), lactulose (0.1 g/kg body weight), and lactose (0.2 g/kg body weight), in aqueous solution made isotonic by the addition of D-glucose. Nothing further was taken by mouth for 5 h except water. During this period, all urine, including that passed at the end of the 5 h, was collected with merthiolate as a preservative, and kept frozen at -20°C.

The urine volume was measured; aliquots were coded and stored frozen. Samples were later analyzed for l-rhamnose, lactulose, and lactose content by thin-layer chromatography, using a modification of the method described by Menzies, Mount, and Wheeler [12], on plastic-backed silica gel layers (Schleicher and Schuell F500) with butanol-1-ethanol-glacial acetic acid:water, 60:30:10:10 v/v (14 cm, ascending) using sucrose and fructose as internal standards. The plates were developed 3 times and were dried between each development. Results were expressed as excretion ratios (the ratio of the proportion of the oral lactulose dose excreted to the proportion of the oral l-rhamnose dose excreted (lactulose/rhamnose ratio), and the ratio of the proportion of the oral lactose dose excreted to the proportion of the oral lactulose dose excreted (lactose/lactulose ratio).

RESULTS

The distribution of lactulose/rhamnose excretion ratios in the 26 eczematous children was significantly elevated compared with
that of the control group, whether the healthy and skin disease control groups were analyzed separately or together \((p < 0.01, \text{ Wilcoxon's ranked sum test, nonpaired, for each comparison})\). However, in 12 of the eczematous children the sugar excretion ratio fell within the range for the healthy children and that published for healthy adults \([13]\) (Fig 1). There were no significant differences between boys and girls or between the 2 control groups.

The lactose/lactulose excretion ratios of the eczematous children did not differ from those of either or both control groups. In no patient was the ratio higher than the published mean \(\pm 2\) SD value for healthy adults \([14]\).

Analysis of clinical and historical data for the eczematous patients showed no association among increased permeability and race, severity of eczema (classified as mild, moderate, severe, or very severe), or oral antihistamine use. In the eczematous group the highest lactulose/rhamnose ratios were found in the younger patients and none of the 6 patients over 8 years of age had increased permeability (Fig 2a). The control groups, though slightly older, did not show a similar relationship of permeability to age (Fig 2b).

Twenty-one of the children were skin-prick tested to common food and airborne allergens. Neither the antigens to which positive immediate responses were obtained nor the diameter of the wheals produced were related to gastrointestinal permeability. In 7 patients total IgE was available and, in these individuals, there was no correlation between this and the urinary sugar ratio, 4 patients having normal and 3 increased permeability. In 15 patients in whom the eosinophil count was measured there was also no correlation between this and the urinary sugar ratio.

Immediate hypersensitivity reactions to foods, such as vomiting, contact urticaria, and angioedema, were reported by 8 children, 4 with increased and 4 with normal permeability. Provocation of eczema by food without a history of food-induced immediate-hypersensitivity reactions was reported in 4 children, 3 with increased and 1 with normal permeability. One child, who had increased permeability, reported both immediate reactions to foods and food-induced eczema.

Thirteen children were on some kind of exclusion diet at the time of the study and, of these, 8 had increased and 5 normal permeability. However, on review, in only 6 of these patients, 3

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**Figure 1.** The ratio of the proportion of the oral dose of lactulose excreted in 5 h, to the proportion of the oral dose of L-rhamnose excreted, in 26 children with atopic eczema and 29 control children. \(\bullet\) = Children with atopic eczema; \(\bigcirc\) = healthy children; \(\square\) = children with psoriasis; \(\blacktriangle\) = children with dystrophic epidermolysis bullosa; \(\blacktriangleleft\) = a child with bullous ichthyoid erythroderma. Horizontal lines indicate \(\pm 2\) SD for healthy adults \([13]\).

**Figure 2.** Lactulose/rhamnose excretion ratio in relation to age in (a) 26 eczematous children and (b) healthy and noneczematous dermatosis control patients. Symbols are as in Fig 1.
from each group, was the eczema judged to have been improved by dietary treatment. The 13 children who were not on dietary treatment at the time (6 with increased and 7 with normal permeability) have been put on diets subsequently. Of these, 10 patients (4 with increased and 6 with normal permeability) showed some benefit.

Three patients reported abnormal gastrointestinal symptoms consisting of mild recurrent abdominal distension and intermittent loose stools with no obvious relationship to food. All three had increased gastrointestinal permeability and one, who had a serum albumin of 16 g/liter, was subsequently discovered to have a protein-losing enteropathy of allergic origin confirmed by 131Cr-labeled albumin studies and jejunal biopsy, and treated successfully with a strict exclusion diet; this child is the subject of a case report [15]. Serum albumin was also measured in 9 other children and in those there was no correlation with the urinary sugar ratio, although the healthy child with a lower than normal serum albumin (30.5 g/liter, normal range 36–52 g/liter) was also 1 of the 3 patients with intermittent gastrointestinal symptoms and an increased permeability; this child has not been investigated for gastrointestinal protein loss.

**DISCUSSION**

These results indicate that a proportion of children with atopic eczema have increased gastrointestinal permeability as judged by the urinary excretion ratio of inert sugar markers. They are at variance with the findings of a smaller study by DuMont, Beach, and Menzies [7], but in agreement with those of Parrilli et al [8]. They are also consistent with the results of Ukabam, Mann, and Cooper [16] using mannitol rather than rhamnose as the smaller sugar marker. Our results show a greater frequency of this abnormality in the younger eczematous child.

These findings do not provide direct evidence for similarly enhanced gastrointestinal uptake of antigen in eczematous patients, since it cannot be assumed that the mechanism for increased lactulose absorption is the same as that for food antigen. The lactulose molecule is much smaller (M, = 342) than intact food proteins, which generally have a M, exceeding 104, although it is known that smaller polypeptide fragments released during protein digestion may be antigenic [17].

The increased gastrointestinal permeability we have shown might reflect mucosal damage induced by local hypersensitivity reactions to foods. Gastrointestinal symptoms are common in children with atopic eczema and are often associated with the ingestion of specific foods, suggesting that allergy may be the cause [18–21]. Furthermore, morphologic abnormalities, in association with impaired maximal gastric acid secretion [22], have been reported in gastric and jejunal biopsies from some children with atopic eczema, findings that were not confined to those with frank gastrointestinal symptoms [20,22]. It was proposed that these changes were allergic in origin.

None of our patients reported gastrointestinal symptoms at the time of urine collection, but some were intermittently subject to such symptoms and others were avoiding foods that had previously provoked them. We performed a jejunal biopsy in one patient in whom there was strong clinical suspicion of malabsorption and this confirmed an allergic enteropathy; there were not felt to be adequate clinical grounds for performing jejunal biopsies in any of the other patients. Lactose/lactulose ratios were normal in all patients, including the one with histologic evidence of enteropathy, suggesting that such mucosal abnormalities as were present were insufficient to cause lactase deficiency.

We examined our patients for evidence of food allergy on the basis of skin tests, history of food-provoked symptoms, and response to exclusion diet and found no association between any of these and increased gastrointestinal permeability. This, and the tendency for younger children in our group to have the highest lactulose/rhamnose ratios, raises the possibility that we are describing a primary abnormality, possibly a delay in gastrointestinal maturation. Increased permeability is normally present at birth, but falls to “adult” values by the 9th day of life [23]. If this early period of enhanced permeability were prolonged, increased exposure to antigen might result and perhaps predispose an individual to the subsequent development of eczema.

It is, however, our view that food allergy remains the most likely cause of the abnormality we have shown. This hypothesis can be tested by the measurement of gastrointestinal permeability before and after successful oral challenge with specific food allergens and before and after totally effective exclusion diets (i.e., diets in which all clinically relevant food allergens can definitely be said to have been excluded). We are, therefore, undertaking such studies at the present time.

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**REFERENCES**


