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For Debate . . .

Rheumatoid arthritis and food: a case study

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Abstract

Clinical and laboratory studies in a patient whose rheumatoid arthritis appeared to be exacerbated by dairy produce showed that challenge with milk and cheese resulted in a pronounced increase in synovitis and changes in immune complexes, IgE antibodies, and heat-damaged red cell clearance rates. Exclusion of dairy produce from the diet produced a considerable improvement in her previously aggressive disease.

Despite an increasing interest in the potentially pathogenic effects of food allergy and despite the conviction of innumerable patients with rheumatoid arthritis that certain foods exacerbate their disease, little scientific attention has been paid to the relation between ingested food antigen and rheumatoid disease activity. Recent studies have shown that the absorption of food antigen may be associated with the development of circulating immune complexes in some patients with IgA deficiency or with food antigen sensitivity as well as in certain normal individuals,[1-3] and that certain non-human proteins such as casein may become deposited in the skin of such people.[4]

As part of a larger study of the effects of certain food proteins on immunological measures in rheumatic disease, we have recently observed a patient in whom the ingestion of cheese and other dairy products had an immediate and profound effect on her clinical and immunological state. Restriction of these foods produced a prolonged improvement in the patient's previously unresponsive arthritis.

Case report

In November 1979 a 38-year-old mother of three children presented with an 11-year history of progressive, erosive seronegative rheumatoid arthritis. Conventional treatment with salicylates and non-steroidal anti-inflammatory agents had failed. Both gold and penicillamine treatment had had to be discontinued owing to mucocutaneous side effects, and prednisolone 10 mg daily (which she was still taking) had failed to relieve the intense synovitis and stiffness. Plasma exchange was tried, and although she obtained some relief this benefit was short lived. Azathioprine was also tried but was stopped because of intestinal upset.

The patient gave a history of multiple drug allergies, including sensitivity to penicillin, as well as the toxic manifestations of gold and penicillamine treatment. She had developed severe gastrointestinal discomfort associated with aspirin, indomethacin, and azathioprine, and rashes related to Elastoplast and detergents. At no time had she experienced respiratory symptoms on exposure to these chemicals, and she had never noticed an exacerbation of her arthritis after such exposure. Her mother (who also has rheumatoid arthritis) was similarly reactive to Elastoplast, penicillin, detergents, and aspirin, and also nickel. Her sister and niece both have asthma.

On examination, she was a pale, unwell young woman with widespread intense synovitis affecting both large and small joints symmetrically. Stiffness as well as fatigue lasted for several hours each day. There were no nodules. There was dryness of the eyes and mouth and a dry Schirmer's test. Grip strengths were weak (110 mm with the left hand and 120 mm with the right hand) and the Ritchie index of articular activity[5] was high at 42. Investigations showed a normochromic, normocytic anaemia of 10·5 g/dl, an erythrocyte sedimentation rate of 110 mm in the first hour, and normal immunoglobulins. IgM rheumatoid factor tests (Latex and sheep cell agglutination) were negative on numerous occasions. Circulating immune complexes as measured by the Clq binding method[6] and the rheumatoid factor binding method were present in a titre of greater than 250 μg equivalents of heat-aggregated human IgG. No cryoprecipitate was detected. C3 concentrations were normal at 96% of normal human serum, and total haemolytic complement activity was 60-90% of normal human serum. Estimates of reticuloendothelial function using clearance of heat-damaged red cells[7] showed prolonged clearance on more than one occasion. Radiographs showed many erosions in the carpus and metacarpal phalangeal joints as well as proximal interphalangeal joints and metatarsal phalangeal joints.

TREATMENT AND PROGRESS

Since her early 20s the patient had had a passion for cheese, consuming up to 1 lb (0·4 kg) a day. Although there was no clear history of allergy or diarrhoea after eating cheese she agreed to try the effect of restricting dairy produce, with the elimination of milk,

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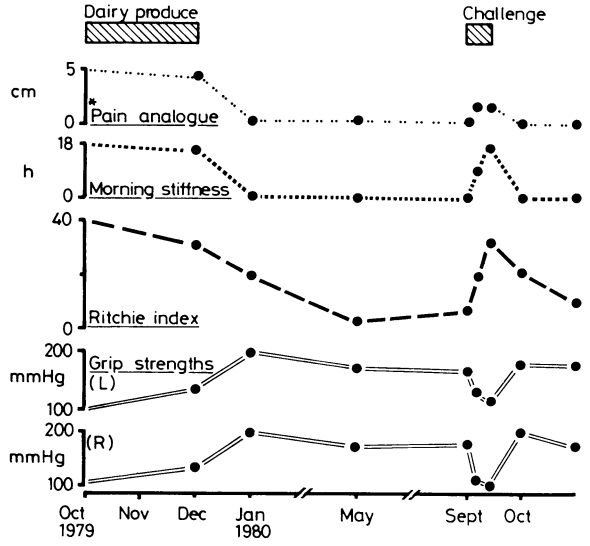
cheese, and butter from her diet. She continued to eat meat, including beef.

Three weeks after starting the diet she began to feel better—both the synovitis and the morning stiffness diminished. She was re-examined frequently over many months, and eventually morning stiffness completely disappeared and the synovitis almost completely resolved. In addition to an improvement in clinical measurements (grip strength, Ritchie index, visual pain analogue score) the erythrocyte sedimentation rate improved and circulating immune complexes disappeared. The improvement was maintained, apart from when she inadvertently ate dairy produce again—after which the symptoms returned within 12 hours. After 10 months the patient agreed to rechallenge tests (see below). Apart from the period after cheese challenge, she has remained well and fully mobile with only minimal residual disease activity, and she has stopped taking prednisone.

FOOD CHALLENGE

The patient was admitted and over three days she consumed 3 lb (1·4 kg) of cheese (Hammersmith Hospital cheddar) and seven pints of milk. Measurements of Ritchie index, grip strengths, morning stiffness, ring size, and visual pain analogue were made before the challenge, 12 hours after the start of the challenge, and daily thereafter. Serial laboratory measurements, including circulating immune complexes (Clq binding method) and IgE antibodies as measured by the radioallergosorbent test (RAST)[8] were also made, the latter kindly performed by Dr J Brostoff and his colleagues. The clearance of heat-damaged red cells as a measurement of splenic function[7] was determined before, during, and after the challenge.

Within 24 hours, there was a pronounced deterioration of the patient's arthritis, with an increase in Ritchie index and morning stiffness and a change of grip strength (figure). The ring size of several



Changes in patient's condition throughout the study period. (Visual pain analogue was measured as normal from 0 to 10 cm, but all measurements recorded were 5 cm or less.)

fingers also changed, the largest increase being a change of 5 mm (or two ring sizes). Laboratory measurements changed, with the development of a leucocytosis and change in concentrations of circulating immune complexes (table). Results of RAST tests for IgE antibodies to milk and cheese protein were negative before the challenge but became positive during the challenge. The highest concentrations were detected 12 days after the challenge was stopped, and on each occasion the reactions with cheese were more strongly positive than those with milk. Results of RAST tests to milk and cheese performed on the synovial fluid remained negative throughout the challenge. The clearance of heat-damaged red cells was normal before the food challenge, but it became considerably prolonged when tested two days and 14 days after the start of the challenge (table).

Changes in patient's condition before and after challenge

	Pre-challenge	End of challenge	12 Days post-challenge	6 Weeks post-challenge
White cell count	7·2	12·3	6·9	6·8
CIC Clq	25 μg AHG	35 μg AHG	50 μg AHG	Neg
RAST				
Milk	Neg	+	+ +	ND
Cheese	Neg	+ +	+ + +	
T/2 clearance of HDRBC	15 min	> 100 min	> 100 min	ND

CIC Clq = Circulating immune complexes as measured by the Clq binding method; μg equivalents/1 ml of heat-aggregated human IgG.
RAST = Radioallergosorbent test.
T/2 clearance HDRBC—Half-life clearance of heat-damaged red blood cells.
ND = Not done.

Comments

This patient did not complain of food intolerance, nor did she manifest any of the usual features of food allergy. Nevertheless, she did develop IgE antibodies, as shown by a positive RAST test when challenged with milk and cheese despite negative results of skin testing with milk antigen and only weakly positive results when tested with cheese. Lessoff *et al*[9] suggested that available tests for milk hypersensitivity are inadequate, as his patients with milk intolerance and allergy showed far fewer positive serum and skin test results than those patients with intolerance to other foods. In his series of 100 food-intolerant and allergic patients he did not describe arthritis as a symptom. Nevertheless, as our case shows, the patient may not relate joint symptoms to the offending food until that antigen is removed from the diet.

Several animal species have increased gut permeability to globulin proteins and macromolecules during the neonatal period.[10] This permeability disappears with the maturation of the intestinal cell.[11] Although human infants are far less dependent on gastrointestinal absorption of proteins for their passive immunity, neonatal sera contain a higher percentage of antibodies to food antigens than do adult sera. The direct association of neonatal exposure to bovine antigen with the later development of childhood eczema and asthma[12] may be an important example of increased antigen absorption with the development of a disease state.

The normal adult intestine is also permeable to macromolecules.[13] Factors affecting absorption of intact macromolecules across the adult gastrointestinal mucosal cell are numerous,[14] but a normal secretory IgA and normal gastrointestinal secretions are most important. Our patient is not IgA deficient, but she does have sicca syndrome, a disease characterised by reduced exocrine secretion.

Although food intolerance often causes bowel symptoms, allergic manifestations such as eczema and migraine occurring outside the gastrointestinal tract are now recognised.[15] Cunningham-Rundles *et al*[3] have described an IgA-deficient child with chronic graft-versus-host disease in whom the concentrations of circulating immune complexes fell by more than 70% when milk was excluded from the diet. Most of these complexes contained bovine milk proteins, and fluorescent antibody staining of skin biopsy samples from the child showed the presence of dense deposits of bovine casein in the dermis.

In our patient food challenge produced only slight alterations in circulating immune complex concentrations but a dramatic impairment of the clearance of heat-damaged red cells. The relation of circulating immune complexes to reticuloendothelial function in this condition is not clear. In a separate study from this unit Elkon *et al*[16] showed no significant change in immune complex concentrations in normal controls or in patients with systemic lupus erythematosus after a standard protein meal.

Whatever the mechanism, in this patient there was a clear clinical response to withdrawal of dairy foods and rechallenge with them. The clinical deterioration seen during rechallenge was accompanied by the development of IgE antibodies to milk and cheese proteins and a prolonged clearance of heat-damaged red cells.

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Personal Paper

The slow miracle*

PHILIP KENT

Time wore on. With relentless stealth the crushing constriction of this grim sickness increased. Weaker and weaker, more and more pain, thinner and thinner. Limbs like matchsticks and a neck scrawny as a turkey's. What is to happen? I have a mounting sense of terrible foreboding. Never before have I felt the like, for with this physical withering has come a cruel sharpening of the mind's edge and I seem to respond and alert to everything with increasing sensitivity.

I am walking through the valley of the shadow.

Nothing helps. My knowledge of treatment is now very extensive. You name it—I've tried it, and I might as well have swallowed a packet of dolly mixtures except that the latter would not have produced the frightening reactions of the former! Perhaps plasmaphoresis? But no, I am not suitable for this. So there's just one thing left—immunosuppressors. Secretly I'd always vowed to avoid these, but here I was taking azathioprine and after a long spin interrupted by pneumonia, which might well not have happened had I not been suppressed, it must be abandoned, unhelpful and so unsafe.

*A sequel to "A very personal view" (14 October 1978, pp 1067-8) in which the impact of the onset of acute rheumatoid arthritis was described.

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"If you really want a miracle," said my loyal friend, "you must try cyclophosphamide. The only miracles I've ever seen in rampant rheumatoid arthritis have followed its use."

But do I believe in miracles? Why, yes, of course. Something happening for which there is no known or understood explanation is miraculous. I believe the miraculous is commonplace and everyday, provided we do not fall into the mistake of expecting every miracle to be as rapid and dramatic as a conjuring trick.

The blind is touched and sees. The paralysed man walks and the dead is suddenly alive again. All miracles. Speed miracles. But what of the pansy seed? Just pick one up between finger and thumb. You cannot? No, of course it's too small. But all we need to do with this tiny thing is give it the support and warmth of moist earth and presently we will be rewarded with a flower the texture of whose petals surpasses any fabric, whose colouring defies artistic imitation, and whose scent has never been trapped in a bottle, and the fading flower bears behind it the promise of eternal life locked in a seed pod. This to me is miraculous. We have not the remotest idea or understanding of the amazing potential spark of life carried in that tiny common seed. Blake wrote:

> "To see a World in a Grain of Sand
> And a Heaven in a Wild Flower,
> Hold Infinity in the palm of your hand
> And Eternity in an hour."

Carefully monitored I started taking cyclophosphamide and time ticked, and ticked, and nothing happened. Nothing bad at