Milk protein allergy – a rare cause of pyrexia of unknown origin in an adult female

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Summary: Milk protein allergy is described in a young adult female patient who presented with fever and malabsorption syndrome. The patient fulfilled Goldman's criteria for the diagnosis of milk protein allergy and responded to an elimination diet.

Introduction

Cow's milk proteins are the most frequently involved agents in food allergy.¹ Clinical manifestations^{1,2} vary and in most cases the gastrointestinal tract is involved. There is evidence that these manifestations are immunologically mediated.³ In addition, respiratory and skin manifestations also occur. Multiple symptoms are common.

This communication draws attention to milk protein allergy as a rare cause of pyrexia of unknown origin (PUO) in an adult patient.

Case report

A 23 year old female presented in March, 1985 with a 7 month history of intermittent fever and 3–7 loose stools daily with no blood or mucous. There was associated crampy epigastric pain. The patient had lost 10 lb in weight in the past 6 months. There was a history of allergic rhinitis for the past 10 years and a past history of angio-oedema. Her mother had a long history of allergic rhinitis, eczema and urticarial rashes following ingestion of fish.

On examination the temperature was 38.5°C over the next 3 weeks in the hospital. Systemic examination was well within normal limits. Sigmoidoscopic examination up to 18 cm revealed normal rectal mucosa.

Investigations showed haemoglobin of 9.2 g/dl, total leucocyte counts of $5 \times 10^9/l$, differential leucocyte count with polymorphs 64%, lymphocytes 30%, monocytes 3% and eosinophils 3%. The erythrocyte sedimentation rate was 52 mm/h and blood film showed normocytic normochromic anaemia with a few macrocytes.

Four consecutive stool examinations revealed occult blood in traces to ++; however no *Entamoeba*

histolytica or giardia cysts or trophozoites were seen. One specimen revealed ova of ascariasis. Repeated stool and blood cultures were sterile. Gastric aspirates (done three times) did not reveal any acid-fast bacilli. Twenty four hour faecal fat done on three consecutive days on a daily intake of 60 g fat averaged 27.7 g. Urinary xylose excretion was normal. Total serum proteins were 42 g/l with an albumin of 20 g/l. There was no proteinuria. Serum protein electrophoresis revealed reduced gammaglobulin. Serum iron was 80 µg/ml with a normal total iron binding capacity of 300 µg/dl. The chest X-ray and barium meal with follow-through were normal. Jejunal biopsy revealed a normal villous pattern with mild increase in lymphocytes and plasma cells in the lamina propria. There was no eosinophilic infiltration. The patient refused to undergo a liver biopsy and bone marrow aspiration. She was empirically started on anti-tuberculous treatment. Following this treatment her temperature rose to 40°C and she developed clinical features suggestive of subacute intestinal obstruction. Conservative management was instituted and in a couple of days the patient's symptoms improved. However, fever and diarrhoea continued and she further lost about 5 lb in weight in spite of anti-tuberculous treatment.

In August, 1985 the patient started passing fresh blood in stools. A repeat sigmoidoscopic examination done up to 25 cm did not show any abnormality. The bleeding stopped spontaneously. At this stage the case history was critically reviewed and she was asked to stop all drugs and dietary elimination therapy was instituted. On stopping milk and milk products the patient had a dramatic improvement within a few days. Her abdominal pain and loose stools stopped and at the end of the 3 weeks she became afebrile.

A few days later, a challenge with diet containing milk caused a recurrence of her abdominal pain, fever and diarrhoea which again subsided within the next few days after eliminating milk products from her diet.

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The patient had the same triad of fever, colicky abdominal pain and loose stools after inadvertently ingesting milk, yoghurt or cheese in December, 1985, January, 1986 and again in June, 1986. A lactose tolerance test during the period of symptoms with a 50 g load showed an abnormal response. Now she does not take milk and milk products, has been asymptomatic since then and maintains a normal life. Repeat lactose tolerance test after 50 g of lactose load done now shows a normal curve. Her haemoglobin is 11.3 g/dl, erythrocyte sedimentation rate 30 mm/h and serum proteins normal.

Discussion

The milk protein allergy of early infancy that disappears after two to three years of age is the best investigated form of food allergy and intolerance. Only 2% of children remain allergic after 6 years of age and it has not been reported in adults.

The major presenting symptoms in this patient were fever, diffuse abdominal pain and diarrhoea. The diagnosis of tuberculosis, the commonest inflammatory bowel disease in our country, could be ruled out in view of the normal chest X-ray, barium examination of small bowel loops, a negative Mantoux test and no response to antitubercular treatment given to her for 8 weeks. Crohn's disease is very rare and could be excluded in view of the normal barium examination and histology of small bowel mucosa. Ulcerative colitis was unlikely in view of the normal rectal mucosa on sigmoidoscopy. The bleeding per rectum was mild, occurred without any alteration of bowel habits and subsided spontaneously.

The diagnosis of milk protein allergy was considered retrospectively after the exclusion of chronic inflammatory bowel diseases, particularly keeping in view that her symptoms disappeared after the exclusion of milk and milk products and recurred after

the reintroduction of milk on four separate occasions.

The major symptoms of milk protein allergy have been reviewed.^{1,2} The clinical symptoms appear immediately after the ingestion of the offending agent and less frequently after 24 hours or even after days of milk intake. In the latter cases, malabsorption is more common. Fever is an unusual feature of milk protein allergy in infants⁴ and has not been reported in adults. She also gave history of frequent episodes of allergic rhinitis and had developed angio-oedema in the past. Co-existent lactose intolerance may be present in some patients² but the fact that the patient could not tolerate even the live yoghurt and has shown a normal lactose tolerance test after her symptoms subsided ruled out the diagnosis of lactose intolerance.

The main stumbling block in the diagnosis of cow's milk protein allergy is the lack of a reliable laboratory test.^{1,4} The cornerstone in diagnosis of cow's milk protein allergy is clinical history and the clinical response to the elimination of milk and milk products and subsequent challenge. The laboratory tests in most cases do not add substantially. This patient fulfilled the criteria proposed by Goldman⁵ which are (i) all symptoms subside completely after elimination of milk from diet, (ii) the symptoms should recur within 48 hours of a trial feed, (iii) this sequence of events should be reproducible on three consecutive occasions with similar course of symptoms. Since lactose or galactose intolerance may also satisfy Goldman's criteria, at least one other manifestation of allergy – such as asthma, rhinitis or eczema is required before the diagnosis of milk protein allergy is accepted.⁴ Many authors^{3,6} now agree upon a single challenge in clinical practice. The promising immunological data in the laboratory involving skin testing, serum IgE antibody determination to food antigens,⁷ and Clq complement binding tests³ can be generally helpful but await confirmation and wider acceptance.

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