SHORT REPORTS

IgA deficiency during D-penicillamine treatment

The most common immunodeficiency is a selective lack of IgA, which is found in about 1/700 in the general population.¹ In some instances family cases are found, but usually IgA deficiency seems to be isolated. Against this background it is of great interest to note that IgA deficiency can be induced by phenytoin.^{2,3} Recently we observed in a girl with Wilson's disease diminishing IgA levels during treatment with penicillamine. This suggests that exogenous factors have a role in IgA deficiency.

Case report

The patient was a 12-year-old previously healthy girl presenting with haemolytic anaemia, succeeded by macroscopic haematuria, oedema of the legs, and severe liver dysfunction with low serum albumin (23 g/l) and definitely raised immunoglobulin concentrations (IgG 28, IgA 9, and IgM 4.2 g/l). Complement factors were depressed: C3 <0.15 g/l and C4 45%. There were also signs of impaired renal function. Blood haemoglobin, leucocytes, and differential counts were normal but the platelet count was reduced to $60-100 \times 10^9/l$. Wilson's disease was diagnosed from the findings of low serum ceruloplasmin concentration (0.025 g/l); the presence of a prominent Kayser-Fleischer ring; a "sunflower" cataract; and a high excretion rate of urinary copper.

D-penicillamine treatment, 1 g daily, was started in October 1975 but was withdrawn after one month because of extensive skin erythema. The drug was reintroduced in a low dose after two weeks together with pyridoxine. The D-penicillamine dosage was slowly increased, but after four months at 0.75 g daily, thrombocytopenia—a platelet count down to $13 \times 10^9/l$ —appeared. A new attempt is now being made to restart D-penicillamine together with corticosteroids.

During D-penicillamine treatment the IgG and IgM concentrations decreased moderately (see figure), whereas the reduction in IgA concentration was drastic. This reached very low levels (0.075 g/l) after four months' treatment. IgE was 24 U/ml at that time. The patient had 55% T-lymphocytes (sheep red-cell-rosette forming cells) and 21% B-lymphocytes (membrane-Ig positive cells). The results of stimulation of the patient's lymphocytes with PHA, ConA, PWM, PPD, and Candida antigen were normal. The last two antigens also induced lymphocyte-mediated inhibition of leucocyte mobility. There was a normal development of Ig-containing cells after PWM stimulation. IgA-containing cells also appeared. The patient had no detectable antibodies against IgA.

Immunoglobulin concentrations in relation to treatment with D-penicillamine.

Discussion

Our suspicion that the D-penicillamine treatment may have caused the IgA deficiency in this case is strengthened by a recent report by Strickland and Leu,⁴ where low IgA levels were found in six out of 40 patients with Wilson's disease, most of whom had been treated with D-penicillamine. IgA deficiency was also suggested by Rimbaud *et al*⁵ on the basis of immunoelectrophoretic analysis in a patient with Wilson's disease treated by D-penicillamine. On the other hand, we

found normal IgA levels in eight patients with Wilson's disease who had been treated with D-penicillamine for up to 14 years (samples kindly supplied by Dr Irmin Sternlieb, Albert Einstein College of Medicine, New York).

Since penicillamine is being increasingly used in treating conditions other than Wilson's disease—for example, rheumatoid arthritis—it may be of importance to analyse further its possible relationship to IgA deficiency.

¹ Bachmann, R, *Scandinavian Journal of Clinical and Laboratory Investigation*, 1965, 17, 316.

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³ Seager, J, *et al*, *Lancet*, 1975, 2, 632.

⁴ Strickland, G T, and Leu, M-L, *Médecine*, 1975, 54, 113.

⁵ Rimbaud, P, *et al*, *Médecine et Chirurgie Digestives*, 1973, 2, 3.

(Accepted 4 November 1976)

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Meningitis due to *Escherichia coli* 09 in a patient with uraemia

Escherichia coli causes meningitis in infants but rarely in adults,¹ in whom it is usually secondary to trauma to the central nervous system¹ and occasionally caused by bacteraemia.² We describe a fatal case of meningitis caused by *E coli* 09, a known urinary pathogen, in a Zambian woman with pyelonephritis.

Case report

A young Zambian woman was admitted to the University Teaching Hospital with a history of vomiting and bloody diarrhoea for three days and of a generalised seizure immediately before admission. She was febrile and comatose, responding only to painful stimuli, and had mild dehydration and deep rapid respiration. There was severe neck rigidity with bilateral extensor plantar responses but no focal neurological signs. The results of laboratory investigations on admission were: haemoglobin 10.5 g/dl; white cell count $14.6 \times 10^9/l$ ($14\,600/mm^3$); serum sodium 137 mmol(mEq)/l; potassium 4.8 mmol(mEq)/l; chloride 98 mmol(mEq)/l; urea 69 mmol/l (415 mg/100 ml); cerebrospinal fluid contained red blood cells $7 \times 10^9/l$ ($7000/mm^3$), white blood cells $4 \times 10^9/l$ ($4000/mm^3$) (polymorphs 80%, lymphocytes 20%), protein 2.8 g/l (280 mg/100 ml); glucose 2.2 mmol/l (40 mg/100 ml). The urine contained moderate amounts of albumin, and innumerable pus cells and red blood cells in the sediment. *E coli* was grown on culture of both the cerebrospinal fluid and the urine. Stool culture showed no pathogens. The *E coli* isolated from the specimen of cerebrospinal fluid and the urine were identical—serogroup 09 motile but H untyped.

The meningitis was treated initially with a high dose of ampicillin, to which gentamicin was added after 36 hours. The blood urea concentration rose steadily, and the patient became increasingly acidotic. Peritoneal dialysis was started 72 hours after admission. This successfully corrected her metabolic abnormalities, but her neurological condition deteriorated despite antibiotic treatment, and the patient died five days after admission.

At necropsy the meninges were found to be thickened and covered with a purulent exudate. The brain was soft, and the cut surface showed congestion and oedema. The ventricles were filled with pus. Both kidneys were small (146 g, r 45 g) with a finely granular surface and adherent capsule. The cortex and medulla were both small, and the renal substance contained several small pus-filled cavities. Histologically the kidneys showed features of membranoproliferative glomerulonephritis with an acute on chronic pyelonephritis. The bladder was small with features of chronic nonspecific

cystitis. The spleen was enlarged and congested with one obvious micro-abscess.

Comment

This patient appears to have had longstanding urinary tract infection in addition to chronic glomerulonephritis. Probably her recent illness developed with an *E coli* bacteraemia originating from the urinary tract, as the central nervous system was seeded with the same strain of *E coli* 09 found in the urine. No enteropathogens were isolated. The septicaemia and uraemia may have accounted for the bloody diarrhoea.²

In view of the frequency with which *E coli* septicaemia occurs in adults it is surprising that *E coli* meningitis is rare. The reason for this is not known,³ though possibly a patient develops *E coli* meningitis only when the immune mechanisms are severely compromised.³ The uraemia in this patient is one possible cause of immunological anergy⁴ and in at least one other report *E coli* meningitis was associated with uraemia.⁵ The mortality of *E coli* meningitis is high,³ partly owing to the difficulty in establishing an early diagnosis.¹ As *E coli* septicaemia and uraemia are not infrequently associated, an awareness of the possibility of meningitis may lead to earlier recognition of this complication.

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³ Zouboulakis, E D, *et al*, *Clinical Paediatrics*, 1972, **11**, 603.

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(Accepted 28 October 1976)

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Subcorneal pustulosis and IgA myelomatosis

Subcorneal pustulosis is a relapsing condition affecting the groins, axillae, submammary areas, and flexor aspects of the limbs. The cause and pathogenesis remain unknown. It has not hitherto been shown to be associated with any other disorder.¹ We describe a patient with subcorneal pustulosis and multiple myelomatosis.

Case report

A man aged 61 presented in 1975 with a blistering eruption over the axillae and upper thighs. In 1970 a moderately well differentiated adenocarcinoma of the sigmoid colon had been resected. Examination showed erythematous areas with crops of small superficial pustules (see figure) over the axillae, thighs, groins, buttocks, and flanks.

Investigations—Skin biopsy: subcorneal pustule, no amyloid, IgA fluorescence throughout section; erythrocyte sedimentation rate 130 mm in first hour (Westergren); haemoglobin 11.1 g/dl; serum proteins: total 71 g/l, paraprotein (IgA- λ ; 37 g/l) serum immunoglobulins: IgG 3.4 g/l, IgM 0.5 g/l; urine: free λ -chains 0.6 g/l; bone marrow: myeloma cells 20% of nucleated cell count; serum complement: CH₅₀ 1225 MU/l (control 1000 MU/l), C3 60% (low), total alternative pathway 140% (normal); no serum autoantibodies present against epidermal intercellular substance or basement membrane zone; antinuclear factor and thyroid, gastric, mitochondrial, and smooth-muscle antibodies not detected; blood urea, electrolytes, urate, Ca⁺⁺, aspartate and alanine transaminases, and cholesterol normal; chest radiograph and skeletal survey normal; no occult blood detected; Wassermann reaction negative; platelet and white cell, and differential counts normal; cryoglobulin absent.

Before myelomatosis was diagnosed he was started on dapsone 100 mg/day with only transient improvement. The dose was increased to 150 mg/day but the haemoglobin fell sharply and the drug was stopped. By this time the diagnosis of myeloma had been confirmed and he was started on intra-

Appearance of eruption over axilla.

venous cyclophosphamide 600 mg/m² every two weeks. He also began a course of sulphapyridine tablets, initially 1 g twice daily. The skin failed to improve until the sulphapyridine had been increased to 4 g/day, at which dose the rash was almost completely suppressed, with only occasional pustulation.

Comment

The aetiology and pathogenesis of subcorneal pustulosis are unknown. It resembles pustular psoriasis of the von Zumbusch type and dermatitis herpetiformis. Abnormalities of the jejunal mucosa, however, which are common in dermatitis herpetiformis, do not occur in subcorneal pustulosis. Antibodies to stratum corneum have been found in pustular psoriasis and pemphigus foliaceus. Using the same technique Krogh and Tönder² studied two patients with subcorneal pustulosis and found antibody to stratum corneum in the roofs of the pustules. No antibody was detected in the blister fluid itself possibly because of depletion, and in one patient the titre of antibody in the serum fell during exacerbations.

The association with multiple myelomatosis in our patient may have been fortuitous, but an IgG cryoglobulin has been found in a patient with subcorneal pustulosis.³ Our patient's myeloma was producing an IgA paraprotein, and abnormalities of serum IgA have been noted in several cutaneous disorders. In psoriasis, one feature of which is pustulation, raised serum concentrations have been reported.⁴ Fraser *et al*⁵ also noted raised serum IgA concentrations in dermatitis herpetiformis, which is characterised by deposits of IgA along the basement membrane zone. Few reports of subcorneal pustulosis give the immunoglobulin values. In most instances they were normal, though Peterson *et al*⁶ noted increased serum IgA concentrations on immunoelectrophoresis in two patients. Thus there is scant evidence to suggest a relationship between IgA and subcorneal pustulosis. Nevertheless, the emergence of an IgA antibody implicated in the pathogenesis of subcorneal pustulosis need not result in a rise in the total serum IgA.

We thank Professor J Hobbs for the immunoglobulin studies.

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³ Sneddon, I B, personal communication.

⁴ Fraser, N G, *et al*, *British Journal of Dermatology*, 1969, **81**, 89.

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(Accepted 28 October 1976)

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