Low plasma cortisol concentrations during late asthmatic responses

Plasma cortisol concentrations in relation to late asthmatic responses after inhalation of allergen have not been reported. We measured serial plasma cortisol concentrations in various types of asthmatic responses.

Patients, methods, and results

Thirteen atopic patients with asthma volunteered to take part in the study. All had a history of episodic dyspnoea with wheezing or chest tightness on exposure to allergens (house dust, *Candida albicans*, and wheat flours). None had received corticosteroids therapeutically. Allergen inhalation tests showed that five of the patients had late asthmatic responses alone, four had immediate asthmatic responses alone, and the remainder had both immediate and late responses.

Heparinised blood samples were obtained before challenge, one and five hours after challenge, and during paroxysm. Plasma cortisol concentrations

Serial changes in mean (SEM) plasma cortisol concentrations in five patients who showed late asthmatic responses alone related to changes in forced expiratory volume in one second. Broken line indicates diurnal plasma cortisol concentrations over same period measured on another day without any inhalation. Concentrations during late responses were significantly lower than these normal concentrations ($p < 0.01$).

Conversion: SI to traditional units—Cortisol: 1 nmol/l $\approx$ 0.036 μ g/100 ml.

were measured by radioimmunoassay based on a competitive binding principle using a gamma coat iodine-125 cortisol radioimmunoassay kit (Travenol, USA).¹

The two types of asthmatic response showed different patterns of cortisol concentrations: concentrations increased slightly during immediate asthmatic responses whereas they decreased during late asthmatic responses. In the five patients who showed a late response the mean cortisol concentration fell from 301 (44) nmol/l (10.9 (1.6) μ g/100 ml) before challenge to 232 (61) nmol/l (8.4 (2.2) μ g/100 ml) at one hour and to 97 (22) nmol/l (3.5 (0.8) μ g/100 ml) during the late response. The concentration during the late response was significantly lower than the normal concentration over the same period ($p < 0.01$) (figure). In the four patients who showed both immediate and late responses the mean cortisol concentration increased slightly from 265 (25) nmol/l (9.6 (0.9) μ g/100 ml) before inhalation to 290 (41) nmol/l (10.5 (1.5) μ g/100 ml) during the immediate response and then fell to 179 (25) nmol/l (6.5 (0.9) μ g/100 ml) one hour later and to 116 (14) nmol/l (4.2 (0.5) μ g/100 ml) during the late response. The concentration during the late response was again lower than the normal concentration over the same period ($p < 0.005$). In the group who showed only an immediate response the mean cortisol concentration was 354 (41) nmol/l (12.8 (1.5) μ g/100 ml) before challenge, 356 (41) nmol/l (12.9 (1.5) μ g/100 ml) during the immediate attacks,

378 (41) nmol/l (13.7 (1.5) μ g/100 ml) after one hour, and 334 (72) nmol/l (12.1 (2.6) μ g/100 ml) after five hours. These concentrations were not significantly different from normal values over the same period.

Comment

The pathophysiological mechanism of late asthmatic responses is still obscure, but premedication with corticosteroids inhibits the development of such responses.^{2,3} This phenomenon caused us to speculate that if adrenal production of steroids is insufficient to block late asthmatic responses the function of the adrenal glands in producing endogenous steroids may be the basis for the responses.⁴

We found that plasma cortisol concentrations were appreciably decreased during late asthmatic responses. This decrease was considered to be specific to late responses as it occurred consistently in the group who showed a late response and during late responses in the group who showed both late and immediate responses but it did not occur during immediate attacks. Moreover, it was a transient phenomenon, concentrations a few days after the test being normal. These findings seem to support our hypothesis, although the reason why the phenomenon was induced could not be explained. Robson and Kilborn reported a reduction in adrenocortical reserve during attacks in continuous asthma.⁵ As the mechanics of the lung in late asthmatic responses are similar to those in continuous asthma a similar reduction in adrenocortical reserve may occur. The pathophysiology of late responses has not been determined, although they have been attributed to several causes—namely, the generation of factors derived from mast cells, the activation of the coagulation cascades, and arachidonic acid products. This study will be of some value in giving a new direction to further research on late asthmatic responses.

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IgA nephropathy associated with mastitis and haematuria

IgA nephropathy accounts for 18% of all cases of primary renal disease, and 60% of patients with the condition present with recurrent macroscopic haematuria.¹ Episodic haematuria often occurs simultaneously with or is closely preceded by pharyngitis or vigorous exercise. We report a patient with IgA nephropathy in whom episodes of macroscopic haematuria showed a close temporal relation with mastitis.

Case report

A 32 year old woman presented with a four year history of microscopic haematuria, which had first been noted on routine analysis of urine during her last pregnancy. On four occasions over this period she had had episodes of mastitis with breast pain and fever accompanied by bilateral dull loin pain and followed within 12 hours by macroscopic haematuria; she was not lactating. All symptoms had resolved within 12 hours of the start of antibiotics on each occasion. Urine cultures were sterile. She had no history of arthralgias, rash, hypertension, or renal, hepatic, or bowel disease and was not taking any drugs. Physical examination yielded normal results, and her blood pressure was 130/70 mm Hg.

Quantitative urine microscopy during remission showed 1×10^8 red blood cells, 15 000 granular casts, and 30 000 red cell casts/l; the urine was sterile on culture. Serum creatinine concentration was 0.09 mmol/l (1 mg/100 ml), creatinine clearance 79.2 ml/min, and urine protein loss 0.38 g/day. Total serum IgA concentration was raised at 4.08 (normal 0.70-3.12) g/day with

normal serum IgG, IgM, and complement concentrations and normal results of serum electrophoresis. Negative or normal results were obtained for hepatitis B surface antigen, rheumatoid factor, antinuclear factor, double stranded DNA antibody, the Venereal Disease Research Laboratory test, anti-streptolysin O titre, and cryoglobulins. An intravenous pyelogram was normal.

Percutaneous renal biopsy showed 37 glomeruli, of which one was completely and some were partially sclerosed. Many showed mild mesangial hyperplasia, and some had capsular adhesions. Many arcuate and interlobular arteries were thicker than normal; there were focal areas of interstitial fibrosis. Immunofluorescence showed moderate granular mesangial deposition of IgA and C3 with moderate granular extraglomerular vessel deposition of C3. Occasional definite mesangial electron dense deposits were seen on electron microscopy.

Comment

This patient had mesangial IgA nephropathy with historical evidence of episodic macroscopic haematuria associated with mastitis. Haematuria associated with pharyngitis has been well documented, but to our knowledge this is the first reported case of haematuria associated with mastitis.

The pathogenesis of this disease is unclear. Circulating immune complexes containing IgA and lymphocytes bearing IgA were both detected in the serum, and there was evidence of decreased IgA specific suppressor T cell activity.^{2,3} IgA is synthesised by submucosal plasma cells in the respiratory and gastrointestinal tracts with increased production after local infection; the secretory component of IgA, however, is absent from glomerular lesions.⁴ The precise mechanism by which pharyngitis is linked to exacerbations of haematuria has not yet been elucidated.

Breast milk and colostrum are rich sources of IgA and the secretory component, which has been synthesised in vivo from cultured colostrum mononuclear cells.⁵ The close temporal association of repeated episodes of mastitis and macroscopic haematuria in this case is supportive evidence for an extrarenal origin of the glomerular IgA deposits.

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Minimal change nephropathy in the acquired immune deficiency syndrome

In patients with the acquired immune deficiency syndrome (AIDS) renal disease is unexpectedly common, focal and segmental glomerulosclerosis being the major cause of heavy proteinuria.¹⁻³ We report the previously undescribed association of minimal change nephropathy with heavy proteinuria in a patient with AIDS.

Case report

A 29 year old heterosexual man from the West Indies was admitted with fever, malaise, and weight loss of several weeks' duration. Two years previously he had developed opportunist infections (cryptococcal meningitis and infection due to herpes simplex virus type II) and been found to have hepatitis B virus e antigenaemia. Renal function had been normal, with no proteinuria. He denied abuse of intravenous drugs and homosexual contact and had never received blood products.

On examination he was febrile and cachectic. There was diffuse alopecia, a macular truncal and perianal rash, and generalised lymphadenopathy. The liver was palpable 5 cm below the costal margin. Funduscopy showed multiple cotton wool spots, and there was left lower quadrantanopia. Investigations showed: urea concentration 4 mmol/l (24 mg/100 ml), creatinine 78 μ mol/l (0.9 mg/100 ml), albumin 27 g/l, alkaline phosphatase 445 IU/l, aspartate transferase 168 IU/l, 24 hour urine protein 3.3-5.9 g, haemoglobin 100 g/l, white cell count 2.2×10^9 /l, lymphocytes 24% (0.5×10^9 /l), and platelet count 184×10^9 /l. A chest x ray film and intravenous urogram were normal.

Percutaneous renal biopsy showed 23 glomeruli: one was totally sclerosed, and 22 showed nil change on light microscopy. There was foot process fusion but no other appreciable abnormality on electron microscopy, and immunoperoxidase was negative for immunoglobulins G, A, and M and for C3. Liver biopsy showed only mild fatty change without evidence of chronic active hepatitis; there were nuclei of bizarre shape but no electron microscopic evidence of viral infection. No infective cause for the fever was found, but a computed tomogram showed multiple intracerebral lesions, found on biopsy to be primary cerebral lymphoma.

During the illness the ratio of T helper to suppressor cells fell from 2.0 to 0.19 (normal range 1-3). During treatment for the lymphoma with deep x ray therapy, daunorubicin, cyclophosphamide, vincristine, and dexamethasone he became severely neutropenic and died of septicaemia. His serum was subsequently found to be positive for antibody to human T cell lymphotropic virus III.

Comment

Proteinuria is common in patients with AIDS. Fourteen patients with mild proteinuria had no light microscopic changes in the glomeruli and lacked typical electron microscopic features of minimal change nephropathy as seen in our patient.⁴ Such mild proteinuria may occur as the result of infection, haemodynamic change, and nephrotoxic drugs.

The occurrence of heavy proteinuria (>3 g/24 hours) in AIDS requires further explanation. Abuse of heroin is typically associated with focal and segmental glomerulosclerosis⁵; indeed, 12 of 21 patients with heavy proteinuria and AIDS abused intravenous drugs, and nine of these had focal and segmental glomerulosclerosis on biopsy.¹⁻³ In the remaining nine patients, however, no cause was identified for their renal disease (focal and segmental glomerulosclerosis in six, mesangial proliferation in three).

Minimal change nephropathy is usually idiopathic but may be associated with an altered immune environment, as in patients with lymphoid tumours. In AIDS the pathogenesis may be lymphokine mediated injury; typical glomerular changes have been induced by supernatant from lymphocyte cultures from patients with idiopathic minimal change lesions.⁶

Our patient did not admit to any of the classical risk factors for AIDS; in view of the initial presentation with genital ulceration, however, the probable source was sexual contact. Neither proteinuria nor evidence of lymphoma was evident at the initial presentation, clinically or on computed tomography. Although minimal change nephrotic syndrome induced by tumour was a possibility, because of the patient's rapid death we could not assess whether treatment of the haematological malignancy would have led to remission of the renal lesion and hence whether the pathogenesis was related to the tumour or to the altered immune state of AIDS.

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