Pure red-cell aplasia: association with systemic lupus erythematosus and primary autoimmune hypothyroidism

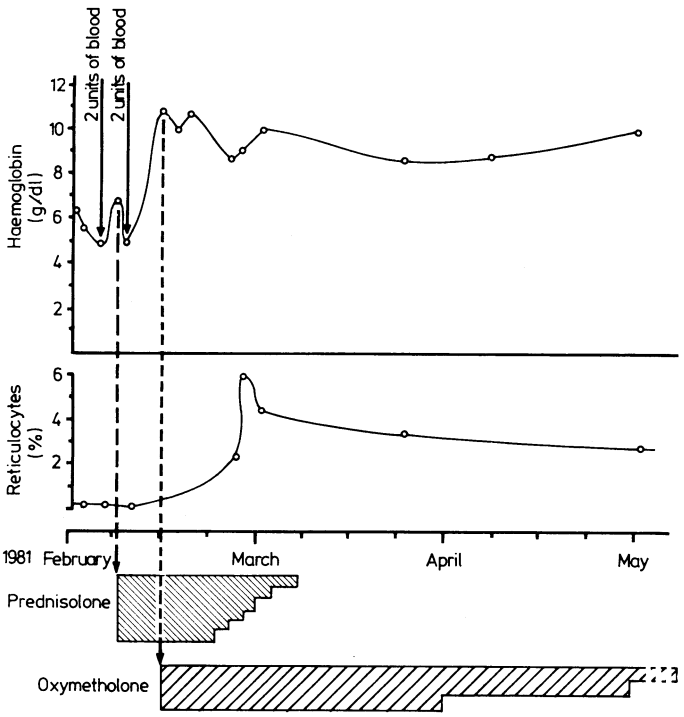
Pure red-cell aplasia has been reported in association with several autoimmune disorders, but not with primary autoimmune hypothyroidism. This report confirms another link between pure red-cell aplasia and altered autoimmunity.

Case report

A 58-year-old woman presented in 1975 with depression and general malaise. Examination showed mild synovitis of the interphalangeal joints of both hands and "butterfly" facial rash. Investigations showed haemoglobin concentration 13·2 g/dl; white cell count $3·4 \times 10^9$/l; erythrocyte sedimentation rate 50 mm in first hour; rheumatoid factor 1/40; antinuclear factor 1/64; DNA binding 38% (normal 10-30%); and serum C3 reduced at 62% pooled normal serum (normal 70-120%). Lupus erythematosus cells were not seen, urine analysis gave negative results, and thyroid function tests were normal. Chest and joint radiology showed no abnormality. Systemic lupus erythematosus was diagnosed and her disease remained quiescent for the next six years.

She then returned with a three-month history of progressive dyspnoea and appreciable lethargy. On examination she was grossly hypothyroid, severely anaemic, and in mild congestive cardiac failure. Investigations showed haemoglobin concentration 6·2 g/dl; mean corpuscular volume 108·6 fl (108·6 pm^3), other variables normal; white cell count $5·8 \times 10^9$/l; platelet count 432×10^9/l; reticulocytes less than 0·1%; direct agglutination test negative; and erythrocyte sedimentation rate 145 mm in first hour. Serum iron concentration was 46 μmol/l (276 μg/100 ml) (normal 13-31 μmol/l); total iron binding capacity was normal. Serum vitamin B_{12} and folate concentrations were normal; and parietal-cell and intrinsic factor antibodies negative. Faecal occult blood tests gave negative results. Other tests showed free thyroxine index one, thyroid-stimulating hormone 60 mU/l (normal 1-10); thyroglobulin antibody 1/2560; thyroid microsomal antibody 1/100; systemic lupus activity quiescent; rheumatoid factor and antinuclear factor titres unchanged; and serum complement concentrations and DNA binding normal.

Despite repeated blood transfusions her haemoglobin concentration dropped to 4·7 g/dl with reticulocytopenia. Bone-marrow aspiration showed the characteristic features of pure red-cell aplasia. Treatment was started with prednisolone 30 mg daily and oxymetholone 3 mg/kg/day. Thyroid supplements were also given. The figure shows the response to treatment. Repeated marrow histology two months later showed an active normoblastic reaction, and despite a suboptimal haemoglobin response her symptomatic recovery was almost complete.



Observed response of pure red-cell aplasia to treatment with prednisolone and oxymetholone.

Comment

Pure red-cell aplasia is characterised by severe normochromic normocytic anaemia with reticulocytopenia in the peripheral blood and absent red-cell precursors in an otherwise normal bone marrow.

An autoimmune aetiology has been proposed for the disease in many patients based on the presence of serum immunoglobulin inhibitors of erythropoiesis and their disappearance on remission with immunosuppressant treatment.[1] In addition, the immune basis for pure red-cell aplasia has been supported by the frequent association of the disease with other immunological conditions including thymoma,[1] systemic lupus erythematosus,[2 3] and multiple endocrine gland insufficiency in which hypofunction of the gonads, parathyroid, and adrenal glands secondary to circulating autoantibodies was noted.[4]

The autoimmune reactions associated with systemic lupus erythematosus often manifest themselves by the peripheral destruction of blood elements giving the well-recognised syndromes of autoimmune haemolytic anaemia and immune-type thrombocytopenia. In rare instances systemic lupus erythematosus has been associated with pure red-cell aplasia, and evidence supports the concept that in this condition the erythroid hypoplasia may be caused by immunological damage to red-cell precursors.[3] The fact that our patient had quiescent systemic lupus erythematosus for six years with no associated anaemia suggests that autoimmune hypothyroidism was the main aetiological factor in precipitating pure red-cell aplasia.

The association of pure red-cell aplasia with altered autoimmunity suggests a defect in the immune surveillance system allowing the unrestrained production of antibodies against certain target organs, which may include red-cell precursors. Our case report, linking this condition with yet another established autoimmune disorder, would seem to support this opinion.

I thank Dr P B L Muldoon, consultant physician, for permission to report this case.

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Reduction of free testosterone by antiepileptic drugs

Sex hormone disturbances have recently been found in epileptic patients treated with drugs.[1-4] Concentrations of sex-hormone-binding globulin were raised in both male and female patients despite normal[2] or increased[3] plasma concentrations of total testosterone. The observation that gonadotrophin concentrations are often increased,[2 3] suggests, however, the possibility that plasma concentrations of unbound (free) sex hormones are abnormally low,[1 3] and this might account for the diminished libido and reduced fertility reported in male epileptic patients.[5]

To study this possibility, we measured plasma concentrations of free testosterone in a group of male epileptic patients receiving chronic antiepileptic drug treatment and a group of matched control subjects.

Patients, methods, and results

We studied 37 male epileptic patients aged 17-40 years who were either residents of the Chalfont Centre for Epilepsy or outpatients at the National Hospital, Queen Square. Most had frequent seizures that were usually complex partial in nature, often with secondary generalisation. None, however, experienced an attack in the 12 hours before the investigations

reported here were performed. They were receiving one or more of the following drugs: carbamazepine, phenytoin, primidone, and sodium valproate. Sixteen healthy male volunteers aged 19 to 40 years and not taking drugs were studied as a control group.

Blood samples were obtained mid-morning. Plasma unbound testosterone was measured by ultrafiltration using purified tritiated testosterone as the radioactive tracer (1, 2, 6, 7-^{3}H testosterone, Amersham International). Sex-hormone-binding globulin was measured by a modification of the method of Rosner and plasma total testosterone by radioimmunoassay using 1, 2, 6, 7-^{3}H testosterone.

The table shows the results of the assays. Concentrations of sex-hormone-binding globulin were significantly higher in the patients than the controls, but plasma total testosterone concentrations remained within the normal range. The free testosterone fraction and the calculated free testosterone concentration were significantly lower in the patients.

Median concentrations (and ranges) of sex-hormone-binding globulin and plasma total testosterone, and calculated free testosterone concentration, in 37 male epileptic patients and 16 controls

	Sex-hormone-binding globulin (nmol/l)	Plasma total testosterone (nmol/l)	Free fraction (%)	Calculated free testosterone (nmol/l)
Epileptic patients	49·0* (10-106)	23·3 (13·0-46·9)	1·4* (0·9-2·5)	0·35* (0·15-0·89)
Controls	23·3 (19-28)	21·0 (14·1-25·5)	2·75 (1·7-3·5)	0·55 (0·40-0·74)

* Significantly different from value in controls ($p < 0.001$, Mann Whitney U test).
Conversion: SI to traditional units—Sex-hormone-binding globulin 1 nmol/l ≈ 29 mg/100 ml. Testosterone: 1 nmol/l ≈ 28·8 mg/100 ml.

Comment

We have confirmed earlier findings[1-4] that concentrations of sex-hormone-binding globulin are raised in drug-treated epileptic patients. In our patients plasma total testosterone concentrations were not significantly different from normal. This observation agrees with our previous findings[2] but contrasts with the raised concentrations found by Toone *et al.*[3] The free testosterone fraction in our patients, and therefore the free concentration of the hormone, was, however, reduced. Evidently measurement of the plasma total testosterone concentration in epileptic patients is not a satisfactory index of androgenic activity; simultaneous measurement of the free fraction is more helpful.

The cause of the reduction of plasma free testosterone concentration is probably a combination of enhanced metabolism from hepatic microsomal enzyme induction by antiepileptic drug treatment and increased binding to higher circulating concentrations of sex-hormone-binding globulin. The possibility that the central control of gonadal function is disturbed must, however, also be considered. Low circulating concentrations of free testosterone may explain the observation that both libido and fertility are low in epileptic patients.[3 5]

We thank Professor Lesley Rees, St Bartholomew's Hospital, London, for advice and for supervising the hormone assays.

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Unexplained acute arthritis in hemiplegia

Prompt exclusion of infection is vital in cases of acute monoarthritis or oligoarthritis, but recognition of arthropathy may be delayed in hemiplegic patients. We report two patients who developed an acute arthropathy soon after a cerebrovascular accident in whom no underlying cause was detected.

Case reports

Case 1—A 66-year-old hypertensive man developed fever and acute arthritis in the right wrist 10 days after the onset of right-sided hemiplegia. Microscopy of synovial fluid showed no bacteria or crystals. Blood and synovial fluid cultures were sterile, but while results were awaited oral antibiotic treatment was started and the joint splinted. Pain and swelling settled over five days and antibiotics were stopped. Fourteen days later he developed acute arthritis in the right ankle, wrist, and second and third metacarpophalangeal joints; on this occasion he was not feverish. Antibiotics were again started on the presumption of sepsis, but aspirate from the acutely inflamed right ankle was sterile and the inflammation subsided rapidly. Six days later arthritis in the right ankle had responded satisfactorily to ibuprofen. There was no leucocytosis at any stage. Erythrocyte sedimentation rate was 20 mm in first hour; the results of biochemical investigations were normal and test results for rheumatoid factor and antinuclear factor negative. Radiography showed no abnormality. Follow-up of one year showed no recrudescence of arthritic symptoms. Mobility continued to be poor and residual hemiparesis severe.

Case 2—A 75-year-old woman developed right hemiplegia and one week later acute arthritis in the right knee. She was not feverish, and aspiration of the knee joint yielded 10 ml of clear synovial fluid, which showed no crystals or bacteria. Culture was sterile, and since she was not acutely ill she was managed conservatively with splinting and ibuprofen. The pain and tenderness settled over three days and did not recur during mobilisation. Laboratory investigations showed no abnormalities. Radiography of the knees showed only minimal osteoarthritic change. Although her mobility was limited by her hemiplegia, her joints remained asymptomatic six months later.

Comment

Acute arthritis in hemiplegic patients is seldom documented. Hermann reported nine cases of unexplained acute inflammatory joint reaction appearing in the early convalescent stage in patients who had suffered cerebrovascular accidents, and emphasised its predilection for the paretic limbs.[1] Our patients had no history of arthritis, and investigation excluded both sepsis and crystal arthropathies. There was no history of diarrhoea or urinary or chest infection, and no skin or eye symptoms.

The cause of the arthropathy in these patients is not known; both could appreciate pain in affected limbs, and it seems unlikely that trauma was the cause of the arthritis. A reactive arthritis to an as yet unidentified trigger remains a possibility.[2] Alternatively, altered vasomotor responses may be relevant. The second patient had minimal radiological evidence of osteoarthritis, but the acute nature of the arthritis was unusual for osteoarthritis. Previous reports have suggested that rheumatoid arthritis in patients with hemiplegia[3 4] or poliomyelitis[5] results in relative sparing of paralytic limbs. The arthritis in these cases, however, affected the hemiplegic side.

Any acute arthropathy should be investigated promptly. The acute unexplained arthritis in our patients resolved completely, but they were not followed up for long enough to determine whether or not this presentation constituted the onset of palindromic rheumatoid arthritis.

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