SHORT REPORTS

Glomerulonephritis in Agammaglobulinaemia

Most patients with glomerulonephritis develop glomerular injury through humoral mechanisms.¹ As patients with agammaglobulinaemia cannot show appreciable humoral response to an antigenic stimulus development of glomerulonephritis is unlikely to result from antibody-mediated injury. Glomerulonephritis which occurred in a patient with Bruton's agammaglobulinaemia prompted this report.

Case Report

A 3-year-old boy suffered from recurrent infections and was found to have persistently low serum gammaglobulins. Diagnosis was further confirmed by the absence of plasma cells in a lymph node biopsied after adequate antigenic challenge. Replacement with human gammaglobulins was started and continued until his death. Six months before death he developed proteinuria (1.0 to 2.0 g per day) and persistent microscopic haematuria. At no point during the illness had he had oedema or hypertension. He was last admitted for dyspnoea, cough, and fever. Repeated urine testing showed 4+ protein, 10-12 red blood cells, and 1-2 granular casts per high-power field. Concentration of blood glucose was 60 mg/100 ml; urea nitrogen 26 mg/100 ml; serum creatinine 0.6 mg/100 ml. The serum β_2 C globulin level was 195 mg/100 ml (normal 125 ± 40 mg/100 ml). Chest x-ray film showed diffuse pulmonary infiltrates with consolidation of both lower lobes. *Haemophilus influenzae* was recovered from cultures of sputum and blood. He died of respiratory failure and shock.

Necropsy findings included profound atrophy of central and peripheral lymphoid organs and absence of plasma cells. Macroscopically the kidneys were normal. On microscopic examination diffuse thickening of basement membranes with occasional splitting was found but the glomeruli were not hypercellular. Focal necrosis with fibrinoid deposition and hyaline capillary thrombosis was noted in some glomeruli. No amyloid deposition was seen with riboflavin-T staining. Electron microscopic examination confirmed that the glomerular basement membranes were thickened, and subendothelial electron dense deposits were present (fig.). No epimembranous deposits were found.

Electron micrograph of the renal glomerulus shows discrete electron dense deposits (*) on the endothelial (endo) side of the glomerular basement membrane (arrows). (Epi. = Epithelial Cells). ($\times 6982$.)

Comment

Persistently low concentrations of gammaglobulins and the absence of plasma cells in regional lymph nodes after antigenic stimulation, which are the two major laboratory criteria for the diagnosis of agammaglobulinaemia,² were noted in our patient.

Aggregated gammaglobulins mimic biologic properties of immune complexes.³ Aggregation and deposition of gammaglobulins administered for therapy could be implicated in starting glomerulonephritis. If this is so, renal lesions would be expected to occur frequently in patients with agammaglobulinaemia who receive long-term replacement therapy with gammaglobulins. We are unaware of any such report. In addition, attempts to induce renal lesions in mice by aggregated globulins have failed.⁴ These observations lessen the likelihood that the aggregated immunoglobulins had a role in the pathogenesis of the renal lesion in our patient.

For recurrent infections, the child had intermittently received antibiotic treatment. Proteinuria and haematuria, however, were unchanged for six months, while no antimicrobials were given. Persistence of urinary abnormalities for such a long time after the drugs were withdrawn argues against an antibiotic-induced lesion.

Thickening of glomerular basement membranes and subendothelial electron dense deposits have been observed in experimental intravascular coagulation.⁵ Our patient's renal lesion had similar morphological features, which suggests that repeated subclinical episodes of intravascular coagulation triggered by recurrent infections and septicemia may have caused the nephropathy. Though we cannot identify the pathogenetic mechanism, the development of glomerulonephritis in an agammaglobulinaemic individual is of interest.

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Vitamin D-resistant Rickets and 25-Hydroxycholecalciferol

Though patients with hypophosphataemic, vitamin D-resistant rickets (V.D.R.R.) have responded biochemically and clinically to 25-hydroxycholecalciferol (25-OHD₃) and 1,25-dihydroxycholecalciferol (1,25-(OH)₂D₃) in short-term trials,¹⁻⁴ few have received long-term treatment. It has been recommended that patients with pathological fractures of long bones should be treated with phosphate and vitamin D⁴⁻⁶ since 25-OHD₃ and 1,25-(OH)₂D₃ do not correct the underlying metabolic defect. We treated a patient with 25-OHD₃ after vitamin D and phosphate had failed to heal his pathological fracture.

Case Report

Though the family of this 18-year-old man were normal in stature and metabolism, he began to limp when he was 6. The next year a brace was put on his left leg for his worsening limp. After five years with the brace he was referred for surgical correction of bilateral genu valgum in March 1968. He was in the 10th percentile for height and had secondary gait abnormalities. Blood urea nitrogen, sodium, potassium, chlorine, CO₂, protein-bound iodine, fasting blood sugar, and serum proteins were normal. Calcium,

phosphate, and alkaline phosphatase are shown in the table. Skeletal x-ray pictures showed the classic changes of rickets with widening of the epiphyseal growth plates and multiple stress fractures of the left foot. An iliac crest biopsy showed a growing epiphysis with endochondral ossification and spongy and cancellous bone but no changes suggestive of rickets, probably because such changes occur earlier in long bones than in the iliac crest. Hypophosphataemic, vitamin D-resistant rickets was diagnosed and treatment with vitamin D 5000 IU was begun.

Treatment with vitamin D and phosphate salts transiently raised his serum phosphate but never altered his alkaline phosphatase significantly (table). He was confined to a wheelchair because of increasing pain and fear that he would sustain a pathological fracture. In March 1969 he underwent supracondylar osteotomy of the left femur to correct the knee deformity, and the limb was immobilized in plaster for three months. The osteotomy site developed some calcified callus but never completely healed. He fractured the proximal third of the left femur while doing quadriceps exercises in bed in June. This fracture was stabilized by an intramedullary rod and spica cast. Over two years his condition worsened and the fracture failed to heal though some bone remodelling around the fracture did occur. In January 1971 multiple fractures of the left tibia and fibula were immobilized in a long leg cast. The intramedullary rod and hip spica were removed in May and the long leg cast in November. The fractures failed to unite, so 25-OHD₃ 100 µg/day was begun in September 1972 to determine whether this vitamin D metabolite would heal the fractures.

After three months' treatment blood values had not changed significantly (table), but radiographs of the wrists showed reossification and narrowing of the growth plates, indicating healing rickets. In January 1973 25-OHD₃ was increased to 200 µg/day in an attempt to establish the maximal dose level without inducing hypercalcaemia. Serum calcium increased and in March the dose was reduced to 140 µg/day. Blood values gradually improved (table), his fractures healed, and he walked for the first time in five years in March 1974.

Representative Serum Values and Treatment

Date	Calcium (mmol/l)	Phosphate (mmol/l)	Alkaline Phosphatase*	Treatment/day
3/68	2.65	0.58	37	Vitamin D 5000-100 000 U, phosphate 1.7 g
11/68	2.60	0.96	30	Vitamin D 5000-100 000 U, phosphate 1.7 g
6/69	2.72	0.77	45	Vitamin D 5000-100 000 U
6/70	2.62	0.77	50	"
5/71	2.47	0.67	1450	Vitamin D 25'000-75'000 U, phosphate 0.75 g
9/72	2.40	0.58	985	25-OHD ₃ 100 µg
1/73	2.32	0.67	800	25-OHD ₃ 200 µg
3/73	2.52	0.83	575	25-OHD ₃ 140 µg
6/73	2.45	1.03	300	"
9/73	2.40	1.16	210	"
2/74	2.47	1.16	185	"

*Alkaline phosphatase was measured in Bodansky units from 3/68 to 6/70 and in International units from 5/71.

Conversion: SI to Traditional Units

Calcium: 1 mmol/l $\approx$ 4 mg/100 ml.

Phosphate: 1 mmol/l $\approx$ 3.1 mg/100 ml.

Discussion

Phosphate supplements during initial treatment with vitamin D raised this patient's serum phosphate, but no radiological improvement of the bones resulted. After treatment with 25-OHD₃ the skeleton reossified, the epiphyseal growth plates closed, and the fractures healed even before serum phosphate changed. Significantly, serum phosphate returned to normal after a year on 25-OHD₃ without phosphate. The alkaline phosphatase also decreased towards normal. Though the skeletal changes began with the start of 25-OHD₃ treatment they also coincided with the attainment of skeletal maturity (age 16½ years). Our results do suggest that 25-OHD₃ may be useful in patients who are unresponsive to vitamin D, especially those with non-union of pathological fractures.

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Oliguric Thrombotic Microangiopathy during the Fifth Month of Pregnancy

Acute renal failure with microangiopathic anaemia (M.H.A.) may develop after apparently normal pregnancy and delivery.¹ In our patient a haemolytic-uraemic syndrome developed at the 22nd week of pregnancy. No improvement of renal function was observed after heparin therapy and persistent malignant hypertension required bilateral nephrectomy.

Case History

The patient was a 23-year-old primigravida who was five months pregnant and admitted in August 1974. Initially her pregnancy had been normal, though she had had mild proteinuria and moderate hypertension at the 16th week. Previous medical history was non-contributory. During the 22nd week of pregnancy pallor, facial petechial purpura, periorbital oedema, and dark-coloured urine were observed. On subsequent examination she was found to have severe hypertension (180/110 mm Hg), oligoanuric renal failure, anaemia, and proteinuria (5 g/l). On admission, blood pressure was 160/190 mm Hg. Fundi and neurological examination were normal. Pulmonary oedema required immediate haemodialysis. A few hours later at caesarean section, performed because of fetal insufficiency, the uterus was normal, though the infant died soon after birth. The postoperative course was complicated by cerebral thrombophlebitis with convulsive seizures and transient pyramidal signs. Laboratory investigations showed: blood urea 47.3 mmol/l (285 mg/100 ml); plasma creatinine 39.8 µmol/l (9.5 mg/100 ml). There were obvious signs of intravascular haemolysis: red cell count $2460 \times 10^9/l$ without schistocytes; haemoglobin 7.6 g/dl; reticulocytes count $130 \times 10^9/l$, serum bilirubin 49.6 µmol/l (2.9 mg/100 ml), haptoglobin level 0.2 g/l. White cell count was $11.5 \times 10^9/l$, platelet count $60 \times 10^9/l$, coagulation factors were normal with plasma fibrin degradation products <8 mg/l. Tests for L.E. cells, Coombs test, and cryoglobulins were negative. Complement studies showed low levels of C3 and C1q. C3 splitting activity was present in the serum. An intravenous pyelogram and renal arteriograms showed normal size kidneys with poor vascularization of the cortical areas. Renal biopsy showed typical lesions of thrombotic microangiopathy,² with thickening of the capillary walls by large pale deposits located on the internal side of the basement membrane, reducing the capillary lumen. In places wrinkling and collapse of the capillary walls were present suggesting ischaemia. Diffuse tubular atrophy was seen, while numerous thrombi were present in the arteriolar lumen. Despite repeated haemodialysis, treatment with prednisolone (2 mg kg⁻¹ day⁻¹), cyclophosphamide (3 mg kg⁻¹ day⁻¹), heparin, and antihypertensive drugs (hydralazine, pindolol, and diazoxide), anuria and haemolysis persisted. Blood pressure remained high with left cardiac failure, recurrent pulmonary oedema, cachexia, and extremely high plasma renin activity. Bilateral nephrectomy was performed on 25 October 1974. Blood pressure returned to normal levels and the patient is now on regular haemodialysis.

Discussion

The clinical and pathological findings are typical of thrombotic microangiopathy with the haemolytic uraemic syndrome,² and there were the usual serum complement abnormalities.³ Several cases of this syndrome have been observed post partum, the onset varying from one day to several weeks. It may also occur while taking oral contraceptives.⁴ Dacie⁵ cites several cases of haemolytic-uraemic syndrome occurring during the final weeks of pregnancy, though so far as we know it has not been reported during the early months. In our patient no other factor than pregnancy can account for triggering M.H.A.; in particular, there were no previous or concurrent bacterial or viral infections, nor had the patient been taking drugs or oral contraceptives before pregnancy.

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