

Short reports

Prostacyclin in severe peripheral vascular disease

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SUMMARY Prostacyclin (prostaglandin I₂, epoprostenol sodium) arrested the progress of gangrene in the feet of a 6 year old boy with familial but otherwise unexplained peripheral vascular disease. Toe regrowth is now occurring at the line of demarcation.

Case report

A previously fit 6 year old boy presented with cold, blue feet. After four days, during which time his condition deteriorated despite warm foot baths and oral inositol nicotinate, he was referred to this hospital. His parents reported six previous episodes of cold painful toes each of which had lasted a few hours. These were not associated with cold weather or illness. A son and granddaughter of the boy's great grandmother had died from unexplained peripheral vascular disease, requiring serial amputations of digits and limbs. By her second marriage, the same great grandmother had had two children, who in middle life experienced episodes of painful discoloured hands and feet.

Examination was normal apart from the feet (Fig. 1). Dorsalis pedis and posterior tibial pulses were normal. The tips of the toes were black. Cold, mottled, dusky skin extended to the middle of the feet on the dorsal and plantar aspects. Toe temperature varied between 22°C and 30°C while forefoot temperature varied between 23°C and 34°C.

Investigations. The investigations showing our diagnostic approach are given in the Table. They were designed to exclude metabolic and coagulation disorders that could have resulted in peripheral vascular disease in a child of this age. Only abnormal results are noted. The erythrocyte sedimentation rate varied with treatment. Plasma viscosity was increased. Fibrinogen fell from 5 g/l to 2 g/l in a week. The raised antistreptolysin O titre, which also fell after a week, is assumed to have been non-specific.



Fig. 1 Day four before prostacyclin treatment.

Treatment and progress. Initial treatment was with intravenous dextran 40 (50 ml per hour), heparin (10 000 units), naftidrofuryl oxalate (Praxilene) (400 mg per 24 hours by continuous infusion), hydrocortisone (200 mg in four divided doses), and low dose aspirin once daily. After six hours of treatment there was no clinical evidence of vasodilation, the black areas were extending, and the feet looked irretrievable.

Prostacyclin was therefore started by a separate venous line at an infusion dose of 2 ng/kg per minute, increasing over 72 hours to 10 ng/kg per minute. The black areas did not advance further after the infusion was started and when the infusion rate was 8 ng/kg per minute generalised vasodilation was noted, forefoot temperature increased, and previously dusky areas reddened. Neither headache nor nausea occurred and blood pressure remained normal. The erythrocyte sedimentation rate fell to 25 mm/hr.

Prostacyclin was stopped after it had been given at a rate of 10 ng/kg per minute for three days. Within 24 hours the feet deteriorated again and the erythrocyte sedimentation rate rose to 138 mm/hr. The infusion was therefore restarted and increased with rapid increments from 2 ng/kg per minute to 10

Table Investigations

Diagnostic category	Test	Result	Test	Result
<i>Haematology</i>	Haemoglobin	N	Erythrocyte sedimentation rate	150-25 mm/hr
	White cell count	..	Platelets	230×10 ⁹ -650×10 ⁹
	Cryoglobulins	..		
<i>Thrombosis and thrombolysis</i>	Platelet aggregation	N	Factor II-XII	N
	Beta thromboglobulin	..	Antithrombin III	..
	Prothrombin time	..	Plasma viscosity	1.87 cps
	Partial thromboplastin time	..		
<i>Fibrinolysis</i>	Plasminogen	N	Alpha 2 antiplasmin	N
	Plasmin	..	Alpha 2 macroglobulins	..
	Euglobulinlysis time	..	Plasmin activators	..
	Fibrin degradation products	..	Protein C activity	..
			Fibrinogen	5 g/l-2 g/l
<i>Autoimmune disorders</i>	Immunoglobulins	N	Autoantibodies	N
	Complement	..	Other immunocomplexes and phase reactants	..
	Rheumatoid factor	..	Antistreptolysin titre	1250-50
	Lupus erythematosus cells	..		
	Cold agglutinins	..		
<i>Metabolic and biochemical</i>	Serial liver enzymes	N	Urine aminoacids	N
	Bone chemistry	..	Organic acids and homocystine	..
	Serial urea and electrolytes, cholesterol lipoproteins, and triglycerides	..		
	Uric acid	..		
<i>Infective</i>	Blood, urine, and throat swab cultures	N	Serial viral titres to cytomegalovirus, herpes, toxoplasma, adenovirus, psittacosis, measles, mycoplasma, and Coxsackie	N

N=negative or normal.

ng/kg per minute over eight hours. The infusion at this dose was continued over a further 10 days and then gradually withdrawn and replaced with oral dipyridamole. While the patient was receiving Prostacyclin all other treatment was stopped. By the 10th day, the ischaemic process seemed to have burned



Fig. 2 Day 19 showing recovery of the forefoot.



Fig. 3 Healthy regrowth of the toes.

itself out (Fig. 2). A thin layer of epidermis separated from the forefoot and proximal toes showing normal skin beneath. Each foot was left with dry gangrene of the distal half of each toe. The boy returned to school two weeks later wearing fitted boots with protective toe caps.

Twelve weeks after discharge, healing was continuing. Viable toe length had increased and had

needed two revisions of boot size. The gangrenous tips were being extruded by the growth of new toe (Fig. 3).

Discussion

We present this case because of the difficulties we experienced planning rational investigation and treatment. In the absence of autoimmune disease, peripheral vascular disease in such a young child is rare.¹ In the presence of rapidly advancing gangrene, comprehensive investigation before treatment was impossible and many of the studies, particularly those of fibrinolysis, were carried out retrospectively.

One of the boy's relatives who had died developed ischaemia in her early teens, and the disease pursued a relentless course. Investigations included most of the above, together with skin biopsies and histological examination of amputated digits. These had failed to indicate a diagnosis. She had been treated with steroid and immunosuppressive drugs, to no avail. The raised fibrinogen, erythrocyte sedimentation rate, and high platelet count in our patient, however, suggested an autoimmune process, despite the absence of circulating immune complexes. He was therefore offered steroid treatment; again with no effect.

In the six years since the relative died, new techniques for the investigation of thrombosis and fibrinolysis have become available in certain centres in the United Kingdom (protein C activity was measured in Amsterdam). The good peripheral pulses in our patient directed our attention to these factors which often affect the microvascular circulation. Antithrombin III and protein C activity are known to be involved in familial disorders, but in both these deficiency states the thrombotic process usually affects bigger vessels, and we were not

surprised that concentrations proved normal. Our investigations could not be carried out before treatment. We hope that this experience will enable us to work early with an established protocol towards a diagnosis should this child relapse.

Prostacyclin is a powerful vasodilator and the most potent known natural inhibitor of platelet aggregation in man. Biological and pharmacological effects were reviewed recently.² There has been considerable experience in the use of Prostacyclin for peripheral vascular disease in adults³ but its use for this purpose in children has not been reported.

We are convinced that the drug saved the feet of this child, and indeed that a less cautious dose increment could possibly have effected more recovery. An infusion rate of 12 ng/kg per minute for several hours caused no side effects. We are similarly greatly impressed by the continued healing and regrowth of the toes several weeks after stopping treatment which seems analogous to the growth of children's digits after partial amputation.⁴

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Hyperbaric oxygenation in peripheral ischaemic lesions in infants

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SUMMARY Acute peripheral arterial occlusion may lead to gangrene, with loss of parts of arms and legs. Three infants with disseminated intravascular clotting developed dark red discoloration of the tips of fingers and toes which progressed proximally. Repeated hyperbaric oxygenation treatments caused regression of the demarcation line and further progression of necrosis stopped.

Acute massive peripheral arterial occlusion secondary to disseminated intravascular clotting is a rare and severe complication in infants which may lead to gangrene and loss of arms and legs, or death. In the past 10 years we treated three infants with this disorder and peripheral ischaemia with hyperbaric oxygenation in an effort to prevent and reverse hypoxic changes. All three patients shared a common clinical course and we report the first patient here.