Defective growth hormone secretion in children with pycnodysostosis and improved linear growth after growth hormone treatment

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Abstract

Short stature is a characteristic feature of pycnodysostosis. We report defective growth hormone secretion in response to provocation and low insulin-like growth factor-I (IGF-I) concentration in five out of six patients with pycnodysostosis. Physiological replacement with growth hormone increased IGF-I concentration and improved linear growth in these children.

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Pycnodysostosis is a rare hereditary bone abnormality characterised by increased bone density, short stature, hypoplasia of the mandible, dysplasia of the skull bones with delayed closure of the fontanelles and separated cranial sutures, partial aplasia of the terminal phalanges, and increased tendency towards pathological fractures.¹⁻⁵ Sex distribution is equal and an autosomal recessive mode of transmission is indicated.⁴⁻⁷ Patients usually have normal mental function and neither anaemia nor cranial nerve compression. In this report we describe growth data and endocrine function of four children with pycnodysostosis and their affected parents.

Methods

Four children with the clinical and radiological features of pycnodysostosis were studied. All were born by spontaneous vaginal delivery at or near term with normal Apgar scoring at 1 and 5 minutes. Three were small for dates. Parental consanguinity was found in all, and two of their fathers were affected by the disease. The specific characteristics of these children included: generalised increase of bone density (4/4), separated cranial sutures (4/4), large fontanelle with delayed closure (4/4), obtuse mandibular angle (4/4), delayed teeth eruption (4/4), malapposed teeth (3/4), enamel hypoplasia (3/4), dysplastic acromial end of the clavicles (3/4), Wörmian bone pattern of the skull (2/4), frontal bossing (3/4), ocular proptosis (3/4), dystrophic nails (3/4), hepatosplenomegaly and moderate anaemia (1/4), and short stature (4/4). Developmental evaluation according to the revised Denver developmental screening test revealed normal motor, fine motor-adaptive, language, and personal-social abilities (4/4).

All the children had normal renal and hepatic function, blood pH and bicarbonate

concentration, and arterial oxygen saturation. They had normal serum calcium, inorganic phosphate, sodium, and potassium concentrations. Blood ammonia and serum lactate concentrations were also normal. Serum alkaline phosphatase was low in two children. Three patients had normal haemoglobin concentration and haemoglobin electrophoretic pattern. One child (MY) with β -thalassaemia trait and partial red blood cell G6PD enzyme deficiency had reticulocytosis and anaemia (haemoglobin 79 g/l) associated with hepatosplenomegaly. Patients were followed up every four to six months with special emphasis on nutritional and auxological data. The height SD score (HtSDS), body mass index (BMI), and height growth velocity (cm/year) were calculated and recorded. Bone age was determined according to Greulich and Pyle.

After an overnight fast (8 hours), a venous sample was withdrawn through a polyethylene catheter inserted in a forearm vein between 8.00 and 9.00 am. The serum was separated by centrifugation and kept frozen at -20°C until analysed for growth hormone, free thyroxine, thyroid stimulating hormone (TSH), cortisol, and insulin-like growth factor-I (IGF-I) concentrations. After obtaining the basal sample, a standard oral clonidine test (0.15 mg/m^2) was performed and serum samples obtained every 30 minutes for two hours for measurement of serum growth hormone. For those who had defective growth hormone release after clonidine, a glucagon stimulation test (0.1 mg/kg intramuscularly) for growth hormone release was performed. Children with defective growth hormone release in the two tests underwent an IGF-I generation test, in which human growth hormone was injected subcutaneously daily for three successive days (0.1 mg/kg) at 8.00 pm and serum IGF-I concentration was measured before the first injection and on the fourth morning. Serum concentrations of testosterone, luteinising hormone, and follicle stimulating hormone were measured in the two adult patients. Human growth hormone and IGF-I were measured by radioimmunoassay, using reagents from Nichols Institute (San Juan Capistrano, CA, USA).

Results

Table 1 shows growth data for the children. HtSDS decreased significantly with age. All the patients had HtSDS below -2 at the end of their first year and below -3 at the end of the third year, irrespective of their birth length. HtSDS was correlated negatively with age ($r =$

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Table 1 Auxological data of children with pycnodysostosis

Patient	At birth			First year			Second year			Third year			Fourth year			Fifth year			Target	
	LSDS	BMI	HC	LSDS	BMI	HC	HtSDS	BMI	HC	HtSDS	BMI	HC	HtSDS	BMI	HC	HtSD	BMI	HC	Ht	HtSDS
AH	0.4	11.8	33.5	-2.1	13.2	40.3	-4.2	12.5	44.8	-4.7	12.4	46.8	-5.7	13.7	48.2	-5.65	15.3	49.7	163	-2.2
NH	0.6	12.2	34.2	-2.8	15.7	40	-3.4	14.9	45.1	-3.4	14.7	47.3	-3.7	14.7	48.8	-3.3	14.1	50	150	-2.3
MY	-2.7	9.7	30.5	-5.8	12.5	41.3	-6.6	9.12	43.5										142	-3.66
NS	-1.35	10.4	31	-3.7	10.8	39.4	-4.97	11.2	41.5	-5.12	11	42.4	-5.12	10.7	43.5				134	-4.67

L = length; Ht = height; SDS = SD score; HC = head circumference (cm); BMI = body mass index.

Table 2 Hormonal data

Patient	Sex	Age (years)	GH-b (µg/l)	GH-p-c (µg/l)	GH-p-G (µg/l)	IGF-I-b (ng/ml)	IGF-I-a (ng/ml)	% Increase
AH	M	5.5	1	5.2	6.7	38	69	81
NH	F	4.5	1.5	14.4	9.8	61	ND	ND
MY	F	2.25	1.5	5.5	3.6	15	49	227
NS	F	3.5	1.5	2.1	1.5	28	62	121
YS	M	35	1.5	4.8	3.9	45	ND	ND
SM	M	42	1.5	3.1	4.2	55	ND	ND

b = basal, p = peak growth hormone (GH) response to clonidine (c) and glucagon (G), IGF-I-b = basal, IGF-I-a = after GH injection.

- 0.603, $p < 0.01$). At birth, three of the four patients were light for dates; in those three, the weight for length was still below the 10th centile at the end of the first, second, and third year of age. BMI was correlated significantly with age ($r = 0.436$, $p < 0.01$). Skeletal age was delayed compared to the corresponding chronological age, at 3.2 (0.9) *v* 4.5 (1.4) years, mean (SD). All patients had a normal karyotype. Computerised tomographic scanning of the hypothalamic-pituitary area was normal in all patients except NS, who had partial empty sella with mild cortical atrophy.

Hormonal data are presented in table 2. All had normal tolerance to oral glucose load (1.75 g/kg), normal thyroid function, and normal 8 hour serum cortisol concentration. Three children and two fathers had defective growth hormone response to clonidine and glucagon provocation (peak $< 7 \mu\text{g/l}$) and low circulating IGF-I concentration. IGF-I concentrations increased significantly after growth hormone treatment for three days, ruling out

the possibility of growth hormone resistance. Adult patients ($n = 2$) had normal gonadotropin and testosterone concentrations.

Growth hormone in physiological doses (15 units/m²/week, divided in daily subcutaneous doses) significantly increased height growth velocity and HtSDS after a year of treatment (fig 1), without accelerating the bone age. Serum phosphate and alkaline phosphatase concentrations increased significantly after growth hormone treatment.

Discussion

Dwarfing is an essential feature of pycnodysostosis. In addition to the sclerosing bone dysplasia affecting the long bones and vertebral column, chronic airway obstruction and hypoxaemia with or without pulmonary hypertension and cor pulmonale, marked anaemia in the variant with visceral manifestations, chromosomal anomalies associated with the disease, and undernutrition secondary to dental abnormalities have been reported and might contribute to growth impairment in these patients.

In this study, defective growth hormone secretion and low IGF-I concentration was found in five out of the six patients studied. The IGF-I generation test ruled out significant resistance to growth hormone, and in two children growth hormone treatment significantly increased circulating IGF-I concentration and improved linear growth. The normal TSH, free thyroxine, and 8 hour cortisol concentrations rule out any significant abnormality of the hypothalamic-pituitary, thyroid, and adrenal axes in these patients. The normal sexual development, fertility, and serum gonadotropin and testosterone concentrations in the two affected adult males are evidence against any abnormality of the hypothalamic-pituitary-gonadal axis.

In summary, many children with pycnodysostosis have defective growth hormone secretion and low IGF-I concentration. Growth hormone treatment improves their linear growth.

Figure 1 Growth velocity (GV) and height standard deviation score (HtSDS) after growth hormone treatment in pycnodysostosis.

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