Pycnodysostosis: Clinical, Radiologic, and Endocrine Evaluation and Linear Growth After Growth Hormone Therapy

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Pycnodysostosis is a rare hereditary bone abnormality with an autosomal recessive mode of inheritance. We report the clinical, radiologic, and endocrine status of 8 children with this rare disease. All patients had the characteristic phenotype of the disorder including short staure (8 of 8), increased bone density (7 of 8), separated cranial sutures (8 of 8), large fontanel with delayed closure (8 of 8), obtuse mandibular angle (8 of 8), delayed teeth eruption (8 of 8), enamel hypoplasia (7 of 8), dysplastic acromial ends of the clavicles (6 of 8), frontal bossing (6 of 8), ocular proptosis (8 of 8), and dysplastic nails (8 of 8). Developmental evaluation according to the revised Denever developmental screening showed normal motor, fine motor-adaptive language, and personal social abilities in all the children. All had normal hepatic and renal functions. Serum calcium and phosphorus concentrations were normal. Two children had low serum alkaline phosphatase concentration. Short stature is a chracteristic feature of pycnodysostosis. Seven of the 8 children were born short (length standard deviation score [SDS] = −3 to −1.5) . Deceleration of linear growth was significant during the first 3 years of life. All the children had height SDS below –3 at the end of their third year of life. Although short stature is a feature of this genetic disorder, defective growth hormone (GH) secretion in response to provocation with clonidine and glucagon was found in 4 of the 8 patients. These 4 patients had pituitary hypoplasia on the magnetic resonance imaging (MRI) of their brain. In addition, 3 of these 4 patients had demyelination of the cerebrum. Patients with pycnodysostosis (n = 8) had low circulating concentrations of insulin-like growth factor-1 (IGF-1) compared with normal age-matched short children with constitutional short stature (CSS). IGF-I increased significantly after injecting GH for 3 days in these patients. Physiologic replacement with GH (18 U/m^2/week) divided in daily evening doses subcutaneousely increased IGF-1 concentration and improved linear growth velocity and height standard deviation scores (HtSDS) in the 4 children with GH deficiency. These data ruled out GH resistance and proved the usefulness of GH therapy in the management of short stature in these patients. In summary, some patients with pycnodysostosis have partial GH deficiency and low IGF-1 concentration. GH therapy markedly increases IGF-I secretion and improves their linear growth. MRI study of the brain including the hypothalamic-pituitary area is recommended in these children because of the high incidence of pituitary hypoplasia and cerebral demyelination.

PYCNODYSOSTOSIS IS A RARE hereditary bone abnormality characterized by increased bone density, hypoplasia of the mandible, dysplasia of skull bones with delayed closure of the fontanels and separated cranial sutures, partial aplasia of the terminal phalanges, and increased tendency towards pathologic fractures.[1-5]

Recently, mutations in the gene encoding cathepsin K (CK), a lysosomal cysteine protease localized exclusively in osteoclasts, were found to be responsible for this disease. CK is secreted into the subosteoclastic space where bone matrix is degraded and has substantial collagenase activity critical for bone remodeling. In vitro studies showed that mutant CK proteins causing pycnodysostosis did not degrade type I collagen, the protein that constitutes 95% of organic bone matrix. Mutations in the CK gene from 8 families identified 7 novel mutations (K52X, G79E, Q190X, Y212C, A277E, A277V, and R312G). Expression of the first proregion missense mutation in a cysteine protease, G79E, resulted in an unstable precursor protein, consistent with misfolding of the proenzyme. Expression of 5 mature region missense defects showed that G146R, A277E, A277V, and R312G precursors were unstable, and no mature proteins or protease activity were detected. The mature Y212C enzyme had markedly decreased activity toward type I collagen and a CK-specific tripeptide substrate, indicating that it was unable to bind collagen triple helix. These results provide evidence that a structural change in the CK protein is involved in the pathogenesis of pycnodysostosis.[6-8]

Sex distribution is equal and an autosomal recessive mode of transmission is indicated.[7-10] Patients usually have normal mentation and neither anemia nor cranial nerve compression. In this report, we describe the clinical and growth data, radiologic features, and endocrine functions in 8 children with pycnodysostosis and their affected parents.

Insulin-like growth factor-I (IGF-I) is a growth hormone (GH)-dependent polypeptide that has a 3-fold function as a mediator of the growth-promoting action of GH, as a potent mitogenic factor, and as a metabolic regulator with insulin-like activity.[8,9] Although GH is the main regulator of IGF-I synthesis,[11,12] nutrition, sex steroids, thyroxine, insulin, and glucocorticoid can modify IGF-I synthesis.[13-22] Alteration of IGF-I regulation may provide an attractive explanation for growth impairment associated with pycnodysostosis. To investigate this issue, we measured the GH response to provocation and the circulating concentration of IGF-I before and after GH injection (IGF-I generation test) in 8 children with pycnodysostosis, 15 prepubertal age-matched normal children with constitutional short stature (CSS), and 10 patients with isolated GH deficiency.

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SUBJECTS AND METHODS

Eight children with the clinical and radiologic features of pycnodysostosis were the subjects of this study. The specific characteristics of these children included: (1) short stature (8 of 8), generalized increase of bone density (7 of 8), separated cranial sutures (8 of 8), large fontanel with delayed closure (8 of 8), obtuse mandibular angle (7 of 8), delayed teeth eruption (8 of 8), enamel hypoplasia (7 of 8), dysplastic acromial ends of the clavicles (6 of 8), frontal bossing (6 of 8), ocular proptosis (8 of 8), and dysplastic nails (8 of 8).

All were born through a spontaneous vaginal delivery at or near term with normal Apgar scoring at 1 and 5 minutes. Six were small for dates. Parental consanguinity was found in all of them, and 2 of their fathers were affected with the disease.

Developmental evaluation according to the revised Denever developmental screening test showed normal motor, fine motor-adaptive, language and personal social abilities in all the affected children.

All the children had normal hepatic and renal functions, blood pH and bicarbonate concentration, and arterial oxygen saturation. They had normal serum calcium (Ca), inorganic phosphate (PO_4), sodium, and potassium concentrations. Serum alkaline phosphatase (ALP) concentration was low in 2 patients. Seven of the 8 children had normal hemoglobin (Hb) electrophoresis pattern. One patient with beta thalassemia trait and partial red blood cells (RBC) glucose-6-phosphate dehydrogenase (G6PD) enzyme activity had reticulocytosis and anemia (Hb, 7.9 g/dL) associated with hepatosplenomegaly. Imaging studies included: (1) a skeletal survey; (2) ultrasound evaluation of the abdomen and pelvis; and (3) magnetic resonance imaging (MRI) of the brain with emphasis on the hypothalamic-pituitary area.

Fifteen prepubertal age-matched children with CSS, age range, 5 to 11 years (with height standard deviation score [HtSDS]) at or below –2 and normal GH response to provocation) and 10 children with isolated GH deficiency (GHD), age range, 6.5 to 10.5 years (GH peak response < 7 μg/L in 2 provocation tests) served as controls. Normal population data were from Tanner et al.[23] The bone age was determined according to Greulich and Pyle atlas.[24]

Patients were followed up every 4 months with special emphasis on nutritional and auxologic data. The HtSDS, body mass index (BMI), and height growth velocity (GV) cm/yr were calculated and recorded. Informed consent was obtained from the parents of all children involved in the study. The ethical committee of Alexandria University approved the study protocol.

Following an overnight fast (8 hours), a venous sample was withdrawn through a polyethylene catheter inserted in a forearm vein between 8 and 9 AM. The serum was separated by centrifugation and kept frozen at -20°C until analyzed for GH, free thyroxine (FT4), thyrotrophin (TSH), cortisol, and IGF-1 concentrations.

After obtaining the basal sample, 2 standard GH provocation tests (oral clonidine [0.15 mg/m^2] and glucagon stimulation test [0.1 mg/kg intramuscular (IM)]) for GH release were performed on 2 separate days, and serum sample obtained every 30 minutes for 2 hours for measurement of serum GH.

All children underwent an IGF-1 generation test. Human GH was injected subcutaneously (SC) daily for 3 successive days (0.1 mg/kg) at 8 PM and serum IGF-1 concentration measured before and on the fourth morning. Serum testosterone concentration was measured in the 2 adult patients.

Human GH and IGF-1 were measured by radioimmunometric assay, using reagents purchased from Nichols Institute (San Juan Capistrano, CA). Intraassay coefficients of variation (CV) averaged 5.8% and 6.6%, respectively, and interassay CV averaged 7.6% and 8.4%, respectively, in the range of GH and IGF-I values detected. Data are presented as mean $\pm$ SD. Statistical analyses were performed using the analysis of variance (ANOVA) test to compare analyte concentrations among groups. The linear regression equation was used to test the relationship between variables. Data are presented as means SD.

RESULTS

Tables 1 and 2 show growth data for children with pycnodysostosis. At birth, 6 of the 8 patients were light for date (2.1 $\pm$ 0.2 kg). Their HtSDS decreased significantly with age. All the patients had length SDS below -2 at the end of their first year and below -3 at the end of third year, irrespective of their birth length. At a mean age of 8.7 $\pm$ 3.4 years, the HtSDS was –4.2 $\pm$ 0.83. The HtSDS was correlated negatively with age (r = -.603, $P < .01$). Skeletal age (6.5 $\pm$ 2.3 years) was delayed compared with the corresponding chronological age (8.7 $\pm$ 3.4 years). All patients had normal karyotype. Children with pycnodysostosis had normal BMI and normal dietary intake, both qualitative and quantitative using the 3-day-recall method.

Figure 1A through I demonstrates the skeletal changes found in our patients including: (Fig 1A and B) brachycephalic skull with basal sclerosis, opened fontanels, wormian bones, hypoplastic maxilla, and obtuse mandibular angle; (Fig 1C and D) failure of fusion of the neural arches, spondylolithiasis, vertebral bodies resembling spools, and thick dense ribs; (Fig 1E and F) increased density with thick cortex involving tibia, femur with partial loss of medullary cavity; (Fig 1G and H) acro-osteolysis and irregularity of the distal fragments of the distal

Table 1. Birth Data and Family History

Patient	Gestational Period Week	Obstetric History	Parents Consang	Affected Parent	Affected Sibling	Growth Data at Birth		
						L (cm)	Wt (kg)	HC (cm)
1	37	NI	1st cousin	Father	None	44	1.88	30.5
2	38	2 abortions	2nd cousin	None	2 (1 died)	46.5	2.1	33.5
3	40	2 abortions	2nd cousin	None	2 (1 died)	51.2	3.22	34.2
4	39	NI	1st cousin	Father	None	47	2.3	31
5	40	1 abortion	1st cousin	None	1	49	2.2	34.2
6	40	1 abortion	1st cousin	None	1	48.5	2.5	35
7	39	NI	1st cousin	None	None	46.5	2.8	34
8	38	NI	1st cousin	None	None	47.5	2.75	34
Mean						47.5	2.5	33.3
SD						2.1	0.43	1.63

Abbreviations: L, length; Wt, weight; HC, head circumference; NI, normal.

Table 2. Anthropometric Data of Patients With Pycnodysostosis

Patient	Age (yr)	HtSDS	BMI (kg/m^2)	HC (cm)	GV Before GH (cm/yr)	GV After GH (1) (cm/yr)	GV After GH (2) (cm/yr)
1	6.5	−4.5	15.2	48.5	3.2	10.1	7.8
2	7.5	−4.3	15.7	49.1	2.5	8.7	7.2
3	12	−3.3	20.5	52	4.1	NA	NA
4	13	−4.1	22	52.5	3.1	11.7	8.8
5	10	−3.55	23.4	51.8	4.3	NA	NA
6	11.5	−5.6	26.4	52	2	7.2	6.2
7	5	−3.3	15.3	49.7	3.4	NA	NA
8	4	−5.1	12.2	48	3.9	NA	NA
Mean	8.7	−4.2	18.8	50.45	3.3	9.4	7.5
SD	3.4	0.83	4.9	1.81	0.79	1.87	1.61

Abbreviations: HC, head circumference; GV, growth velocity cm/yr; 1, after the first year; 2, after the second year of GH therapy; NA, not analyzed because of poor compliance with the treatment.

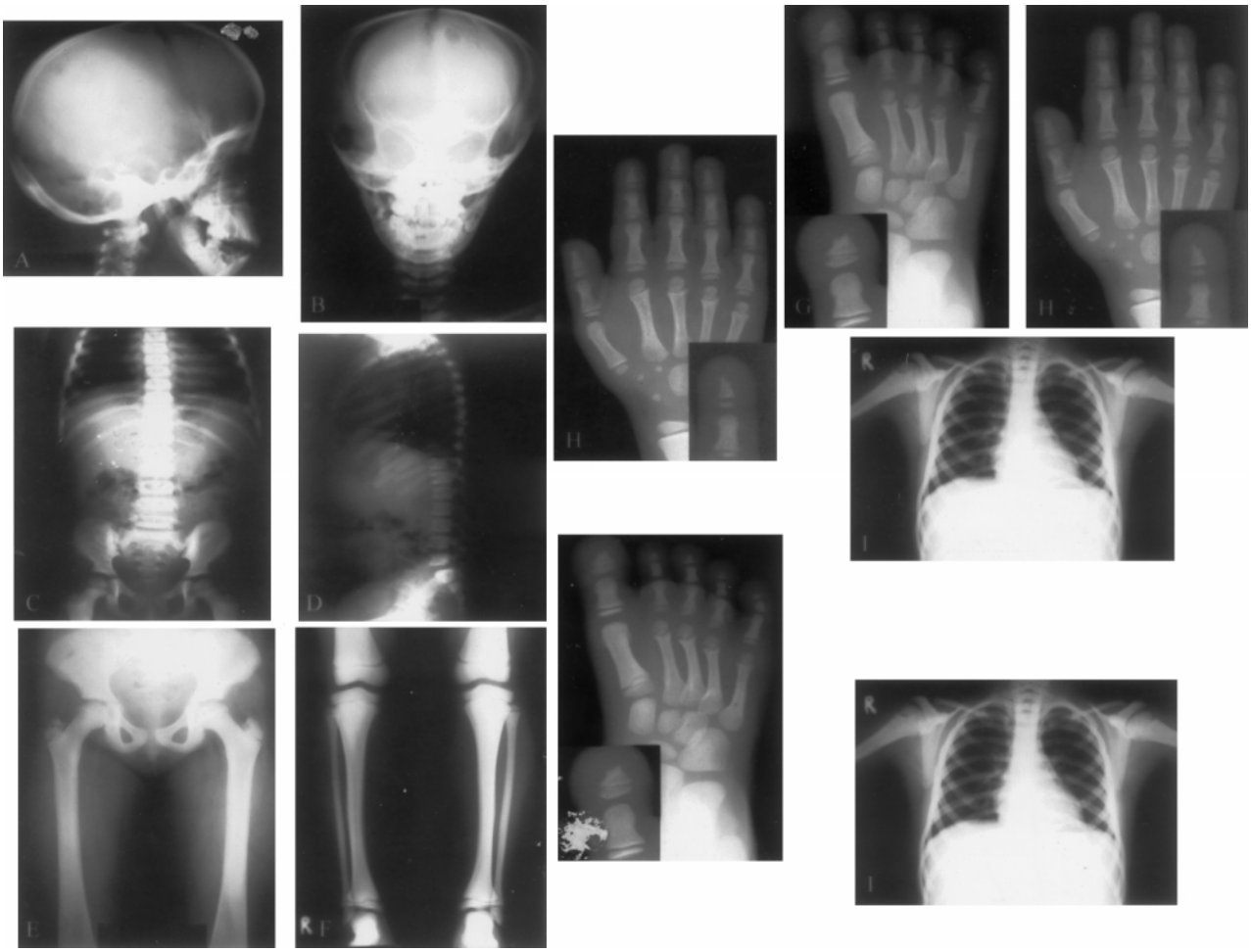

Fig 1. Demonstrates the skeletal changes found in our patients including: (A and B) brachycephalic skull with basal sclerosis, opened fontanels, wormian bones, hypoplastic maxilla, and obtuse mandibular angle; (C and D) failure of fusion of the neural arches, spondylolithiasis, vertebral bodies resembling spools, and thick dense ribs; (E and F) increased density with thick cortex involving tibia, femur with partial loss of medullary cavity; (G and H) acro-osteolysis and irregularity of the distal fragments of the distal phalanges (hand and foot); and (I) hypoplasia of the lateral ends of the clavicles.

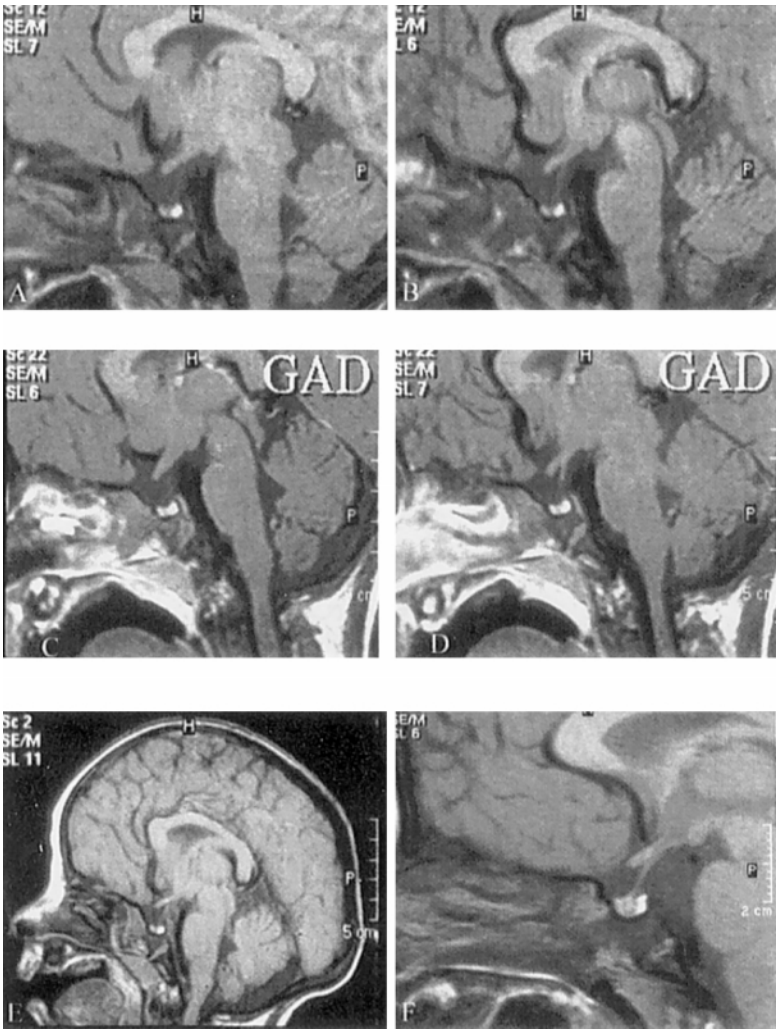

Fig 2. MRI of the brain including the hypothalamic-pituitary area with and without GAD revealed hypoplasia of the anterior pituitary with loss of volume (between 120 to 290 μL) (A and B), borderline pituitary volume (450 to 550 μL) (C, D, and E) and normal volume (550 to 1050 μL) (F).

phalanges (hand and foot); and (Fig 1I) hypoplasia of the lateral ends of the clavicles.

MRI of the brain including the hypothalamic-pituitary area with and without GAD (Fig 2A through F) showed hypoplasia of the anterior pituitary with loss of volume (between 120 to 290 μL) in 4 patients, borderline pituitary volume (450 to 550 μL) in 2 patients, and normal volume in 2 patients (550 to 1050 μL). Significant hypointense appearance (demyelination) of the white matter of the cerebrum, more manifested at the subcortical regions of the brain in both T1- and T2-weighted images, with normal ventricular system, was detected in 3 of the 8 patients (Fig 3A through F). The 4 patients who had hypoplasia of the pituitary showed defective GH release in response to provocation. However, this demyelination had no significant effect on the intellectual functions, motor or sensory systems, reflexes, or coordination of the affected patients. Developmental evaluation according to the revised Denever developmental screening showed normal motor, fine motor-adaptive language, and personal social abilities in all the patients with pycnodysostosis.

The 2 adult males entered puberty (testicular and penile enlargement) at 13 and 14 years of age. They had (n = 2) normal testicular volume and testosterone concentrations (640 and 760 ng/mL). One girl aged 13.5 years had breast development (Tanner IV) and had her menarche at 13 years of age with normal uterine and ovarian size for her pubertal stage.

Hormonal data are presented in Tables 3, 4, and 5. All children had normal tolerance to oral glucose load (1.75 g/kg), normal thyroid function, and normal 8-hour serum cortisol concentrations. Four children and 2 fathers had defective GH response to clonidine and glucagon provocation (peak $<$ 7 μg/L). All patients with pycnodysostosis had significantly low circulating IGF-1 concentrations compared with age-matched children with CSS. IGF-1 concentrations increased significantly after GH injections daily for 3 days ruling out the possibility of GH resistance. However, both basal and GH-stimulated IGF-I concentrations were significantly lower than those for age-matched children with GHD and those with CSS.

In children with pycnodysostosis and GH deficiency (n = 4), GH therapy in physiologic doses (0.1 U/kg/day) (0.1 mg/kg/week) divided in daily SC doses, significantly increased GV and HtSDS during the 2 years of therapy with GH without

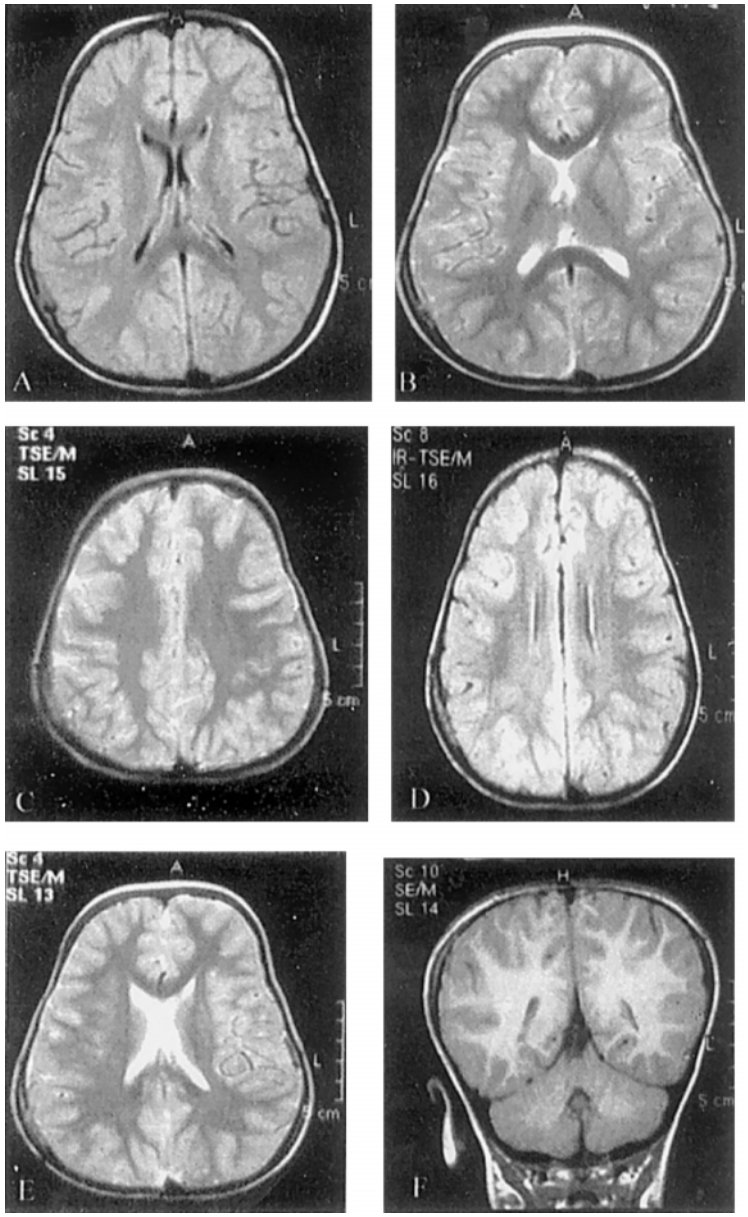

Fig 3. Axial MRI of the brain (T1 W, TR500/TE20) (A and D) and (T2W, TR1200, TE80) (B, C, and E) showing significant hypointense appearance (demyelination) of the white matter of the cerebrum, more manifested at the subcortical regions of the brain, with normal ventricular system. (F) Coronal T1W, TR500/TE20 demonstrating normal myelination of the white matter of one patient.

significant acceleration of the bone age (the other 4 patients were offered GH therapy, however due to poor compliance with the treatment, their data after GH treatment were not analyzed). Linear growth velocity increments for the treated patients was comparable to those with GHD and CSS receiving GH treatment despite their lower IGF-I increments after therapy (Table 5).

DISCUSSION

Dwarfism is an essential feature of pycnodysostosis. In addition to the sclerosing bone dysplasia (affecting the long bones and vertebral column), chronic airway obstruction and hypoxemia, instrinsic short stature, chromosomal anomalies associated with the disease, undernutrition secondary to dental abnormalities and endocrinopathies might be implicated in the etiology of dwarfism in these patients.

In this study, children with pycnodysostosis had normal BMI (18.8 ± 4.9) and normal dietary intake (both qualitative and quantitative) using the 3-day-recall method, despite the presence of dental abnormalities. They had normal renal and hepatic functions and karyotype. Their normal circulating TSH, FT4, and 8-hour cortisol concentrations ruled out abnormalities of the hypothalamic-pituitary thyroid and adrenal axes. The normal sexual development, testicular volume, fertility, and serum testosterone concentration in adult patients spoke against an abnormality of their hypothalamic-pituitary gonadal axis.

Defective GH secretion accompanied by hypoplasia of the pituitary gland was detected in 4 of the 8 children with pycno-

Table 3. Hormonal Data of Patients With Pycnodysostosis (with and without GHD) and Controls

Patients	Cortisol (nmol/L)	TSH (mIU/mL)	FT4 (pmol/L)	GH-Basal (μg/L)	GH After Clonidine (μg/L)	GH After Glucagon (μg/L)	IGF-I (basal) (ng/mL)	IGF-I After GH (ng/mL)	% Increase
Pycno with GHD (n = 4)									
Mean	530.5	2	17.45	1.77	4.5	4.1	26	58.5	141
SD	69	0.29	2.32	0.91	1.6	2.2	9.6	9.8	62
Pycno with normal GH (n = 4)									
Mean	439	1.92	17.7	1.45	12.9	11.7	38.25	65.5	85
SD	16.5	0.3	1.12	0.5	2.5	2.05	18.5	19.8	37
All patients with Pycno (n = 8)									
Mean	467	1.97	17.6	1.6	8.7*	7.9*	32.1*	62*	113
SD	82	0.56	1.99	0.7	4.88	4.46	15.1	14.7	56
CSS (n = 15)									
Mean	499	2.3	16.9	1.85	18.6	16.7	142	212	50*
SD	99	0.5	1.6	0.75	2.7	3.7	49	58	35
GHD (n = 10)									
Mean	412	1.5	15.8	0.7	4.2*	3.9*	66	159	141
SD	65	0.25	1.4	0.3	0.9	1.5	25	52	56

NOTE. Cortisol, 8 AM cortisol; IGF-I after GH, after 3 days of GH injection (IGF-I Generation test).

* $P < .05$ among groups.

dysostosis. This was previously reported by us in a smaller number of patients.[25] Histologic and radiographic analysis of the mice deficient in the CK gene showed osteopetrosis of the long bones and vertebrae and abnormal joint morphology. X-ray microcomputerized tomography images showed increased bone volume, trabecular thickness, and trabecular number in both the primary spongiosa and the metaphysis of the proximal tibia. Encroachment on the bone marrow cavity resulted in abnormalities in hematopoietic compartments, particularly decreased bone marrow cellularity and splenomegaly. Similarly, pressure by the increased bone volume on the pituitary might explain, in part, the finding of pituitary hypoplasia and partial GH deficiency in some of these patients.[26] It is postulated that because the walls of the sella turcica are relatively rigid, the increased bone volume (involving the sellar wall in pycnodysostosis) might increase intrasellar pressure (ISP), which in turn, impairs portal blood flow, resulting in hypopituitarism. Increased ISP has been recently shown to be a major mechanism involved in the pathogenesis of hypopituitarism. Increased ISP leads to compression of the portal vessels and the associated interruption of the delivery of hypothalamic hormones to the anterior pituitary.[27] This might explain the GH deficiency in these cases. In addition, increased ISP may also lead to decreased blood supply, resulting in ischemic necrosis in some regions of the pituitary. The latter could explain the development of pituitary hypoplasia in some of these patients.

Table 4. Hormonal Data of Patients and Controls (means ± SD)

	Pycnodysostosis (n = 8)	CSS (n = 15)	GHD (n = 10)
IGF-I (ng/mL) before GH	32 ± 15*	153 ± 42	56 ± 25†
IGF-I (ng/mL) after GH	62 ± 14.6*	226 ± 45.5	158 ± 50†
IGF-I (ng/mL) change	29.9 ± 3.35*	73 ± 11.7	95 ± 24
Peak GH to clonidine	8.7 ± 4.88*	18.6 ± 2.7	4.2 ± 0.9†
Peak GH to glucagon	7.9 ± 4.6*	16.7 ± 3.7	3.9 ± 1.5†

* $P < .01$ pycnodysostosis *v* CSS.

† $P < .01$ GHD *v* CSS.

All children with pycnodysostosis had significantly decreased circulating concentrations of IGF-I compared with age-matched children with CSS. All the children studied (except 1 [patient 7] had BMI below the 5th percentile for age) with pycnodysostosis had BMI at or greater than the 50th percentile for age and sex. This excluded undernutrition as a factor contributing to low IGF-I in these children. Significant IGF-I increments after GH injection (IGF-I generation test) (n = 8) and after a year of GH therapy (n = 4) ruled out significant resistance to GH in these patients. In support of this view, GH therapy significantly improved linear growth velocity for 2 years (9.4 ± 2.1 cm/yr and 7.5 ± .1. cm/yr during the first and second years, respectively) versus before treatment (3.3 ± 0.8 cm/yr). Linear growth velocity increments for the treated patients was comparable to those with GHD and CSS receiving GH treatment despite their lower IGF-I increments after therapy. These differences in IGF-I levels might be due to differences in binding proteins (not measured in this study). GH therapy effectively increased the HtSDS in the 4 patients treated for 2 years without an adverse effect on bone age. Three patients had significant demyelination of the cerebrum without significant effect on the intellectual or motor functions during childhood.

In summary, many patients with pycnodysostosis have defective GH secretion and low IGF-I concentrations. GH therapy markedly increases IGF-I secretion and improves their linear growth. MRI study of the brain including the hypothalamic-pituitary area is recommended in these children because of the high incidence of pituitary hypoplasia and cerebral demyelination.

Table 5. Anthropometric and IGF-I Data Before and After GH Therapy (means ± SD)

	Age (yr)	GV (1) (cm/yr)	GV (2) (cm/yr)	GV Increment (cm/yr)	HtSDS (1)	HtSDS (2)	IGF-I (1) (ng/mL)	IGF-I (2) (ng/mL)
Pycnodysostosis (n = 4)								
Mean	8	3.3*	9.4	6.1	(−)4.7*	(−)3.9*	26*†	79*†
SD	3.4	0.8	1.8	1.1	0.64	0.5	9.6	11.4
CSS (n = 8)								
Mean	6.8	4.5	9.9	5.3	(−)2.6*	(−)1.8*	142	246
SD	1.7	0.4	1.2	0.4	0.4	0.42	49	58
GHD (n = 10)								
Mean	7.3	3.7	10.6	6.9	(−)3.4	(−)2.6	66	189
SD	1.8	1	1.5	1.2	0.5	0.4	25	52

Abbreviations: GV, growth velocity, (1) and (2) before and after GH therapy for 1 year, respectively; CSS, constitutional short stature; GHD, growth hormone deficiency.

* $P < .01$ pycnodysostosis *v* CSS.

† $P < .01$ pycnodysostosis *v* GHD.

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