Empty Sellae, Impaired Testosterone Secretion, and Defective Hypothalamic-Pituitary Growth and Gonadal Axes in Children With Bardet-Biedl Syndrome

Ashraf T. Soliman, Anna Rajab, Issa AlSalmi, and Maurice G. Asfour

We evaluated growth parameters and hypothalamic-pituitary-gonadal and growth functions in five children with Bardet-Biedl syndrome (BBS). Three of the five children had stature below the fifth percentile for age. Their growth hormone (GH) response to provocation was defective, and computed tomographic (CT) scanning revealed empty sellae in all of them. All the children were obese (body mass index [BMI] > 95th percentile for age). Three had hypercholesterolemia. Their basal serum testosterone concentration and testosterone response to 3-day human chorionic gonadotropin (HCG) stimulation were significantly lower than the levels in 12 age-matched obese normal children. Testosterone secretion failed to respond to HCG therapy for 4 weeks. Both basal gonadotropin levels (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and gonadotropin responses to LH-releasing hormone (LHRH) stimulation were normal and did not differ among the two study groups. It appears that primary hypogonadism is a cardinal feature of BBS, and it may be accompanied by hypothalamic and pituitary abnormalities.

LAURENCE-MOON-BIEDL syndrome has traditionally been described as being characterized by retinal dystrophy, polydactyly, obesity, mental retardation, spastic paraparesis, and hypogonadism.[1,2] Harnett et al[3] reported that the syndrome includes the presence of characteristic renal abnormalities. It is suggested that this syndrome comprises two disorders: the Laurence-Moon syndrome and the Bardet-Biedl syndrome (BBS).[4-6] In the former, polydactyly is rare and spastic paraparesis dominates, whereas neurologic complications are very unusual in the latter.[6] Variability of expression of the cardinal features of BBS has been reported.[2,7-9] However, the characteristic features of BBS are severe retinal dystrophy, dysmorphic extremities, obesity, renal abnormalities, and male hypogenitalism.[10] Few investigations have been undertaken to determine the cause of hypogonadism in these patients,[11-13] especially in children and adolescents.

In this study, we described the spectrum of the disease in five prepubertal boys with BBS and investigated their hypothalamic-pituitary function.

SUBJECTS AND METHODS

Five obese boys with the characteristic features of BBS[10] were initially diagnosed in the Obesity Clinic of the Royal Hospital, Muscat, Oman. Four had severe pseudoacanthosis nigricans. They were admitted to the Pediatric Department of the Royal Hospital for investigation. Informed consent was obtained from the parents of the patients and controls.

On admission to the hospital, a 24-hour urine collection was started to measure urine volume, creatinine level, electrolyte levels, and protein excretion. Measurements were made for height, weight, and head circumference. Height standard deviation scores (HtSDS) were calculated according to the formula, HtSDS = (X1 − X2)/SD, where X2 and SD are the age-matched population mean height and SD, respectively, and X1 is the subject height. Growth velocity standard deviation scores (GVSDS) were calculated according to the formula, GVSDS = (X3 − X4)/SD, where X4 and SD are the age-matched population mean height growth velocity and SD, respectively, and X3 is the subject growth velocity. Normal population data were from Tanner.[14] Body mass indices (BMIs) were calculated and recorded. The stage of sexual maturation was assessed according to Tanner staging.[14] On the second morning, abdominal ultrasonographic examination was performed followed by intravenous (IV) pyelography, and blood was drawn for measurement of serum testosterone levels. Combined testing of pituitary function was undertaken. Clonidine (0.15 mg/m^2 orally), thyrotropin (TSH)-releasing hormone ([TRH] 200 μg), and gonadotropin-releasing hormone (Factrel 100 μg; Monomouth Pharmaceutical, Guildford, UK) were administered IV over a period of 2 to 5 minutes. Blood was drawn for measurement of growth hormone (GH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels at 0, 30, 60, 90, and 120 minutes, and for measurement of prolactin (Prl) and TSH at 0, 30, and 60 minutes. Serum cortisol concentration was measured at 8 AM. On the third day, serum and urine osmolality was measured after 8 hours of water deprivation. On the fourth morning, an oral glucose tolerance test (dextrose 1.75 g/kg) and skeletal survey and computed tomographic (CT) scan of the hypothalamic-pituitary area were performed. On the fifth day, blood was withdrawn for estimation of serum testosterone, and human chorionic gonadotropin ([HCG] 3,000 U/m^2) was administered intramuscularly (IM) daily for 3 days. On the morning of the eighth day, serum was collected for estimation of testosterone concentrations and an IV glucagon test was performed (glucagon 15 μg/kg IV). Plasma was collected for estimation of C-peptide before and 6 minutes after glucagon injection. A standard glucagon stimulation test (glucagon 1 mg IM) was performed with pyridostigmine (in children with subnormal GH response to clonidine) to investigate the reversibility of the attenuated GH release in response to glucagon.[15,16] Twelve obese age-matched (BMI > 95th percentile for age) boys served as controls.

Human GH and insulin-like growth factor-I (IGF-I) levels were measured by radioimmunometric assay using reagents purchased from Nichols Institute (San Juan Capistrano, CA), with mean intraassay and interassay coefficient of variations (CVs) of 6.8% and 8.3%, respectively, for GH and less than 9% and less than 10%, respectively, for IGF-I. Free thyroxine (FT_4) TSH, and cortisol levels were measured using Amerlex radioimmunoassay kits (Kodak Clinical Diagnostics, Amersham, UK). LH and FSH

From the Departments of Pediatrics and Endocrinology, Royal Hospital, Muscat, Oman.

Submitted October 23, 1995; accepted April 11, 1996.

Address reprint requests to Ashraf T. Soliman, MD, Chief, Pediatric Endocrinology, Royal Hospital, PO Box 1331, Muscat 111, Oman.

0026-0495/96/4510-0007$03.00/0

Table 1. Clinical Presentation of Children With BBS

Subject No.	MR	Retinopathy	Nystagmus	Polydactyly/ Syndactyly	Small Genitals	Cryptorchid	Obesity	CRF	Hypertension	CT Brain
1	+	+	+	+	+	+ unilaterally	+	–	–	Normal
2	+	+	–	+	+	+ unilaterally	+	–	–	Empty sellae
3	+	+	–	+	+	+ unilaterally	+	–	–	Empty sellae
4	+	+	+	+	+	–	+	++*	+	Empty sellae
5	+	+	+	+	+	–	+	+†	+	ND

Abbreviations/symbols: +, present; –, absent; obesity (+), BMI >95th % for age; CRF, chronic renal failure; (+), creatinine clearance <45 mL/min/1.73 m², (++), <15 mL/min/1.73 m²; hypertension (+), diastolic blood pressure >95th % for age; MR, mental retardation.

*Membranoproliferative glomerulopathy and interstitial nephritis.

†Interstitial nephritis and vesicoureteral reflux.

levels were measured using an immunoradiometric assay kit (Radium; Pomezia, Rome, Italy). The mean intraassay and interassay CVs were 4.8% and 5.8%, respectively. Testosterone level was measured by direct radioimmunoassay using a kit (Diagnostic Products, Los Angeles, CA), with intraassay and interassay CVs of 8% and less. Skeletal age was determined according to the atlas of Greulich and Pyle.[16a]

RESULTS

Table 1 presents the cardinal features of the syndrome in these five boys. All have some degree of mental retardation (five of five), retinal dystrophy (five of five), polydactyly/syndactyly (five of five), small testes and penile length (five of five), and obesity (five of five). Some of them had unilateral cryptorchidism (three of five), hypospadius (one of five), renal disease (two of five), renal impairment (two of five), and hypertension (two of five). CT scan of the hypothalamic-pituitary area revealed normal-size empty sellae in three of these four boys (75%).

Table 2 shows biochemical data for the patients. Children with BBS had borderline-high or high serum cholesterol (three of five) but normal tolerance to an oral glucose load. Two brothers (subjects no. 4 and 5) had impaired renal function. Despite normal glucose tolerance, these patients had high fasting and glucagon-provoked C-peptide concentrations. The renal disease of subject no. 4 was rapidly progressive, and he required renal transplantation at the age of 12.5 years. Histopathological examination of renal biopsy specimens showed membranoproliferative glomerulopathy and interstitial fibrosis in subject no. 4, and interstitial infiltration and fibrosis in subject no. 5. An IV pyelogram and micturating cystography showed caliceal clubbing in both children, with mild vesicoureteral reflux in subject no. 5. The hemogram and serum calcium, phosphate, alkaline phosphatase, and bicarbonate concentrations were normal in all the children. Values for urine osmolality (mmol/L)/serum osmolality (mmol/L) after a 10-hour overnight fast were 487/278, 510/283, and 399/286 in three patients without renal impairment (subjects no. 1, 2, and 3, respectively).

Table 3 presents anthropometric data and GH/IGF-I results for the patients. Three patients had stature below the fifth percentile for age and gender, and only one child had slow annual growth velocity (subject no. 3, <fifth percentile). The GH response to chemical provocation was blunted in three of five children, and was not reversible in response to pyridostigmine. IGF-I concentration was significantly low in two of these children. Basal (8 AM) and peak (after corticotropin) serum cortisol levels were normal in all the patients. Bone age was delayed in four of five (1.2 ± 0.7 years).

Table 4 shows pubertal stage and hormonal data for the children. All had a significantly low basal serum testosterone concentration and a low testosterone response to 3-day HCG stimulation. They had normal LH and FSH responses to LH-releasing hormone (LHRH) stimulation. None of the children had a high basal FSH or an exaggerated response of gonadotropins to LHRH stimulation. All had a normal FT_4 concentration and a normal TSH response to TRH stimulation. Serum Prl concentration was normal in all the children. HCG therapy (2,500 U/m²) IM twice weekly for 4 weeks did not significantly change the testicular size, position of undescended testes, or penile size.

Table 5 compares children with BBS (n = 5) with age-matched obese controls (n = 12). HtSDS were significantly higher in obese normal children versus those with BBS. Serum glucose and C-peptide levels did not differ among the two groups. Gonadotropin levels, either basally or after

Table 2. Biochemical and Hematological Data for the Patients

Subject No.	TG (mmol/L)	Cholesterol (mmol/L)	Glucose (mmol/L)			C-Peptide (ng/mL)		Urea (mmol/L)	Creatinine (nmol/L)	HCO_3 (mmol/L)	U/S Osm (mmol/mmol)
			Baseline	1 h	2 h	Basal	Peak				
1	2.6	6.6	4.1	5.9	5.2	3.2	9.3	4	54	24	1.75
2	2.5	4.6	4.5	4.9	3.5	3.9	7.2	2.8	48	23	1.8
3	2.5	4.5	4.2	5.9	5.1	4.3	11.5	3.4	58	23	1.4
4	3.3	5.2	4.6	6.7	7.1	2.9	8.4	13.5	214	22	ND
5	4.7	6.5	3.2	7.9	6.4	4.2	9.3	10.7	121	21	ND
Normal	0.4-2.5	3-4.7	3.7-6	<10	<8.6	1.3-2.5		2.3-6.7	25-67	22-30	>2

Abbreviations: TG, triglyceride; U/S Osm, urine/serum osmolality after 10 hours of water deprivation; ND, not determined.

Table 3. Growth and GH/IGF-I Data for Children With BBS

Subject No.	Age (yr)	BMI (kg/m²)	SA (m²)	HtSDS	GVSDS	GH (μg/L) Basal	GH (μg/L) Peak	IGF-I (ng/mL)	8 AM Cortisol (nmol/L)	Bone Age (yr)
1	8	24.8	1.24	0.57	0.5	2.5	11.5	210	345	8
2	6	23.7	0.86	−1.85	1.07	1.7	5.3	65	425	4.5
3	7	26.6	0.91	−2.1	−2.2	0.5	2.1	65	340	6
4	11	38	1.49	−2	0.03	1.7	2.7	215	368	9.5
5	14	39.4	2.05	−0.44	1	2.5	8.9	325	458	12
Mean	9.2	30.5	1.31	−1.3	0.08	1.78	6.1	176	387	8
SD	3.2	6.8	0.43	0.8	1.3	0.82	4.03	111	52	2.6

NOTE. Normal range: IGF-I, 135 to 430 ng/mL; cortisol, 200 to 720 nmol/L.
Abbreviation: SA, surface area.

stimulation, did not differ between the two groups. Serum testosterone was significantly lower in children with BBS.

DISCUSSION

Short stature and delayed sexual maturation are features present in children with BBS. Delayed growth might be an inherent part of the syndrome; however, impaired GH/IGH-I secretion may contribute to slow growth in these children. The defective testosterone secretion in these boys might add to their growth impairment by delaying the pubertal growth spurt. Data from the longitudinal study by Stanhope et al[17] suggest that serum testosterone concentrations must be elevated toward the normal adult male range for a considerable proportion of the 24-hour period before an increase in serum GH secretion can be recorded. This change in GH secretion parallels pubertal growth acceleration.[18] Moreover, children with GH insufficiency not treated with exogenous GH attain only 50% to 66% of the expected pubertal growth spurt.[19,20] The presence of chronic renal dysfunction in some children with BBS might also contribute to their growth delay.

The finding of normal-size empty sellae in some children with BBS has not been previously reported. This suggested that empty sellae might be a component manifestation of this syndrome. Michaels et al[21] reported significant endocrine abnormalities in patients with normal-size empty sellae. The most common associations are male secondary hypogonadism, adrenal insufficiency, hypothyroidism, and GH deficiency. Other less frequent abnormalities include GH deficiency and increased β-LH and α-LH with TRH stimulation. In support of this view, Cacciari et al[22] concluded from their study of 339 children and adolescents with possible hypothalamic-pituitary disorders that empty sellae are usually associated with hypofunction or hyperfunction of the hypothalamic-pituitary-gonadal axis. However, normal-size empty sellae are found in a considerable number of normal short children with normal hypothalamic-pituitary function.[23] The contribution of empty sellae to the etiology of hypogonadism in BBS is not known.

In adults with BBS, Green et al[10] reported normal basal LH (seven of eight) and FSH (five of eight) concentrations in some patients and high LH (one of eight) and FSH (three of eight) in others. FSH responses to LHRH were within the normal range in all patients, but both normal (five of eight) and exaggerated (three of eight) LH responses were obtained. Toledo et al[13] and Perez-Palacios et al[24] reported normal basal and LHRH-stimulated LH and FSH levels in three adults and two prepubertal boys who had low testosterone secretion. In one patient, testosterone secretion was normal in the presence of a high basal LH level and an exaggerated LH response to LHRH stimulation. In three adult females, Chang et al[25] reported the failure of estradiol to induce an increase of LH or to modulate gonadotropin release in response to stimulation with LHRH, indicating an absence of a positive-feedback effect of estrogen on LH secretion. FSH levels became undetectable during estradiol administration, suggesting an intact negative-feedback effect of estrogen. In two studies, testosterone secretion was low after HCG stimulation for 3 to 4 days.[13,24] These findings suggest that the hypogonadism associated with BBS can be attributed to primary gonadal failure with or without hypothalamic-pituitary dysfunction.

In our study of prepubertal boys with BBS, basal and HCG-provoked testosterone secretion was significantly decreased compared with that in age-matched obese boys. The response of the testes and secondary sexual character-

Table 4. Hypothalamic-Pituitary Gonadal and Thyroid Axes in Children With BBS

Subject No.	Age (yr)	PS	TD (cm)	Testosterone (nmol/L) Basal	HCG-4d	HCG-4 wk	HCG-N	LH (IU/L) Basal	Peak	Peak-N	FSH (IU/L) Basal	Peak	Peak-N	FT_4 (pmol/L)	TSH (mIU/L) Basal	Peak	Prl (pmol/L)
1	8	1	1.2	0.7	0.7	0.7	22.9 ± 7.7	3.2	4.3	16 ± 12	2.1	6.2	8.6 ± 5.4	12.1	1.9	13	125
2	6	1	1	0.7	1.2	1.6	21.3 ± 7.6	2.6	7.8	6.6 ± 3	1	4.4	12 ± 9	13.3	2.3	11.5	110
3	7	1	0.5	0.7	0.7	0.8	22.9 ± 7.7	2.1	5.8	6.6 ± 3	1.7	3.2	12 ± 9	17.2	1.6	10.5	95
4	11	1	1	0.7	3.8	8.2	26.2 ± 11.5	0.5	5.6	16 ± 12	1.5	8.5	8.6 ± 5.4	18.4	1.2	8.3	275
5	14	1	1.5	0.7	1.2	2.1	21.6 ± 4.2	2.1	4.5	16 ± 12	1.7	4.1	8.6 ± 5.4	15.2	3.5	13.5	159

Abbreviations: PS, pubertal stage; TD, largest testicular diameter; HCG-4d, after HCG for 4 days; HCG-4w, after HCG for 4 weeks; N, laboratory normal data adjusted for age.

Table 5. Comparison Between BBS Subjects and Obese Controls

Parameter	Obese (n = 12)	BBS (n = 5)
Age (yr)	10.1 ± 1.8	9.2 ± 2.9
BMI	31.8 ± 3.9	30.5 ± 6.8
HtSDS	0.9 ± 0.4*	−1.3 ± 0.8
Systolic BP (mm Hg)	124 ± 15	129 ± 12
Diastolic BP (mm Hg)	79 ± 3.4	82 ± 5
[Glucose (mmol/L)]		
0 min	4.95 ± 0.9	4.1 ± 0.5
60 min	6.3 ± 1.4	6.3 ± 1
120 min	6.3 ± 1.1	5.5 ± 1.2
C-peptide (ng/mL)		
0 min	3.44 ± 1.6	3.7 ± 0.55
Peak	8.3 ± 3.2	9.14 ± 1.4
Cortisol 8 AM (nmol/L)	398 ± 114	387 ± 52
Testosterone (ng/dL)	6.5 ± 3.8*	0.7 ± 0.01
LH (IU/L)		
Basal	3.7 ± 1.6	2.1 ± 0.9
Peak	7.1 ± 2.5	5.6 ± 1.25
FSH (IU/L)		
Basal	2.7 ± 0.86	1.6 ± 0.35
Peak	6.2 ± 2.5	5.3 ± 1.9
Prl (mIU/mL)	111 ± 27	152 ± 65
Triglyceride (mmol/L)	1.43 ± 0.5	3.12 ± 0.85*
Cholesterol (mmol/L)	5.05 ± 1.1	5.48 ± 0.9
FT_4 (pmol/L)	15.9 ± 3.75	15.24 ± 2.34
TSH (mIU/mL)	3.5 ± 1.1	2.1 ± 0.8

Abbreviation: BP, blood pressure.
*$P < .05$.

istics to a long course of HCG therapy for 4 weeks in patients with BBS was negligible. In children with impaired Leydig cell function, gonadotropin levels increase both before and after puberty.[24] However, some patients with testicular failure, eg, Klinefelter's syndrome, had a normal basal gonadotropin level and gonadotropin response to LHRH.[26,27] Sizonenko et al[28] compared testicular function in boys with unilateral and bilateral cryptorchidism. Bilaterally cryptorchid boys had normal basal serum FSH levels but supernormal FSH responses to LHRH, whereas no abnormalities of FSH secretion could be detected in the unilaterally cryptorchid boys. In our patients, as in some adults with the disease, despite low testosterone secretion, the basal gonadotropin concentration and the gonadotropin response to LHRH stimulation were normal. These findings suggest that a lack of an increase in LH is due to the coexistence of a hypothalamic disorder of gonadotropin-releasing hormone secretion with a primary testicular failure.

In concert with this view, in one study testicular biopsy in three patients showed a nonuniform degenerative lesion of the seminiferous tubules with marked reduction of spermatogenic activity. Only scant groups of Leydig cells were seen in the interstitium, with a clear decrease in the total number of these cells. The pathology involving the seminiferous tubules and the diminution of Leydig cells appeared progressive with age, suggesting an evolutionary nature of the testicular failure that might progress throughout adult life.[13]

Obesity is a characteristic feature of BBS, as confirmed in other large series.[2,7] In our patients with BBS and the obese controls, despite normal oral glucose tolerance, basal and glucagon-stimulated C-peptide concentrations were high, reflecting a hyperinsulinemic status. This finding indicates that obesity is the major determining factor of this hyperinsulinemia, since it occurred both in patients and in normal obese children. Four patients (80%) had severe pseudoacanthosis nigricans, which is a reliable cutaneous marker of insulin resistance.[29,30] In patients with renal dysfunction, an elevation of C-peptide concentration might be secondary to an impaired clearance of C-peptide by the kidney. The hypercholesterolemia (three of five), hypertriglyceridemia (five of five), and hyperinsulinemia (five of five) reported in these children are important risk factors for cardiovascular disease in such patients.

On the basis of our studies, it appears that boys with BBS may have a dual defect of the hypothalamic-pituitary-testicular axis. They have primary hypogonadism with inappropriately normal basal and LHRH-stimulated gonadotropin levels, indicating hypothalamic and/or pituitary dysfunction. Some of them have short stature and empty sellae, with defective GH responses to stimulation and low IGF-I concentrations.

REFERENCES

1. McKusick VA: Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes (ed 8). Baltimore, MD, Johns Hopkins University Press, 1988, p 834

2. Ammann F: Investigations cliniques et genetiques sur le syndrome de Bardet-Biedl en Suisse. J Genet Hum 18:1-310, 1970 (suppl)

3. Harnett JD, Green JS, Cramer BC: The spectrum of renal disease in Laurence-Moon-Biedl syndrome. N Engl J Med 319:615-618, 1988

4. Bardet G: Sur un syndrome d'obesite congenitale avec polydactylie et retinite pigmentaire (contribution a l'etude des formes cliniques de l'obesite hypophysaire). Doctoral thesis, University of Paris, Paris, France, 1920

5. Schachat AP, Maumenee IH: Bardet-Biedl syndrome and related disorders. Arch Ophthalmol 100:285-288, 1982

6. Farag TI, Teebi AS: Bardet-Beidl and Laurence-Moon-Biedl syndromes in a mixed Arab population. Clin Genet 33:78-82, 1988

7. Bell J: The Laurence-Moon syndrome, in Penrose LS (ed): The Treasury of Human Inheritance, part III, vol 5. London, UK, Cambridge University Press, 1958, pp 51-96

8. Stigglebout W: The Bardet-Biedl syndrome: Including Hutchinson-Laurence-Moon syndrome, in Vinkin PJ, Bruyn GW (eds): Handbook of Clinical Neurology, vol 13: Neuroretinal Degeneration. Amsterdam, The Netherlands, Lea & Febiger, 1972, pp 380-412

9. Bergsma DR, Brown KS: Assessment of ophthalmologic, endocrinologic and genetic findings in the Bardet-Biedl syndrome. Birth Defects 11:132-136, 1975

10. Green JS, Parfrey PS, Harnett JD, et al: The cardinal manifestations of Bardet-Biedl syndrome. N Engl J Med 321:1002-1009, 1989

11. Mozaffarian G, Nakhjavani MK, Farrahi A: The Laurence-Moon-Bardet-Biedl syndrome: Unresponsiveness to the action of testosterone, a possible mechanism. Fertil Steril 31:417-422, 1979

12. Campo RV, Aaberg TM: Ocular and systemic manifestations of the Bardet-Biedl syndrome. Am J Ophthalmol 94:750-756, 1982

13. Toledo SP, Medeiros-Neto GA, Knobel M, et al: Evaluation of the hypothalamic-pituitary-gonadal function in the Bardet-Biedl syndrome. Metabolism 26:1277-1291, 1977

14. Tanner JM: Growth at Adolescence (ed 2). Oxford, England, Blackwell Scientific, 1962, pp 88-102

15. Ghigo E, Mazza E, Corrias A, et al: Effect of cholinergic enhancement by pyridostigmine on growth hormone secretion in obese adults and children. Metabolism 38:631-633, 1989

16. De Marinis L, Mancini A, Zuppi P, et al: Influence of pyridostigmine on growth hormone (GH) response to GH-releasing hormone pre- and postprandially in normal and obese subjects. J Clin Endocrinol Metab 74:1253-1257, 1992

16a. Greulich WW, Pyle SI: Radiographic Atlas of Skeletal Development of the Hand and Wrist (ed 2). Stanford, CA, Stanford University, 1959

17. Stanhope R, Pringle PJ, Brook CGD: The mechanism of the adolescent growth spurt induced by low dose pulsatile GnRH treatment. Clin Endocrinol (Oxf) 28:83-87, 1988

18. Wennick JMB, Delemarre-Van de Waal HA, Shoemaker R: Growth hormone secretion patterns in relation to LH and testosterone secretion throughout normal male puberty. Acta Endocrinol (Copenh) 123:263-267, 1990

19. Aynsley-Green A, Zachmann M, Prader A: Interrelation of the therapeutic effects of growth hormone and testosterone on growth in hypopituitarism. J Pediatr 89:992-996, 1976

20. Tanner JM, Whithouse RH, Hughes PCR: Relative importance of growth hormone and sex steroids for growth at puberty of trunk length, limb length and muscle width in growth hormone deficient children. J Pediatr 89:1000-1005, 1976

21. Michaels R, Robinson D, Sollock R, et al: Dynamic pituitary function and bone density measurement in normal size empty sella syndrome. 75th Annual Meeting, The Endocrine Society, Las Vegas, NV, June 9-12, 1993 (abstr 1613C)

22. Cacciari E, Zucchini S, Ambrosetto P, et al: Empty sella in children and adolescents with possible hypothalamic-pituitary disorders. J Clin Endocrinol Metab 78:767-771, 1994

23. Soliman AT, Darwish A, Asfour MG: Empty sella in short children with and without hypothalamic-pituitary abnormalities. Indian J Pediatr 62:75-81, 1995

24. Perez-Palacios G, Uribe M, Scaglia H, et al: Pituitary and gonadal function in patients with the Laurence-Moon-Biedl syndrome. Acta Endocrinol (Copenh) 84:191-199, 1977

25. Chang J, Davidson BJ, Carlson HE: Hypogonadotropic hypogonadism associated with retinitis pigmentosa in a female sibship: Evidence for gonadotropic deficiency. J Clin Endocrinol Metab 53:1179-1183, 1981

26. Behar BRM, Mendilaharzu H, Rivarola MA, et al: Gonadotrophin secretion in prepubertal and pubertal primary hypogonadism: Response to LH-RH. J Clin Endocrinol Metab 41:1070-1075, 1975

27. Illig R, Tolksdorf M, Murset G, et al: LH and FSH response to synthetic LH-RH in children and adolescents with Turner's and Klinefelter's syndrome. Helv Paediatr Acta 30:221-231, 1975

28. Sizonenko PC, Schindler AM, Roland W, et al: FSH. III. Evidence for a possible prepubertal regulation of its secretion by the seminiferous tubules in cryptorchid boys. J Clin Endocrinol Metab 46:301-308, 1977

29. Flier JS: Metabolic significance of acanthosis nigricans. Arch Dermatol 121:193-194, 1985

30. Khan RC, Flier JS, Bar RS: The syndromes of insulin resistance and acanthosis nigricans. N Engl J Med 294:739-745, 1976