

# Hypothalamo-pituitary hormone insufficiency associated with cleft lip and palate

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**SUMMARY** Two male patients with congenital cleft lip and palate first seen at ages 10.2 and 21.5 years presented with typical signs of hypothalamic-anterior pituitary hormone deficiencies. They were found to lack GH, LH, and FSH and to be partially deficient in TSH and ACTH. Several congenital defects may explain this rare syndrome affecting midline structures in the proximity of the maldeveloped palate, including Rathke's pouch, which migrates distally to develop into the anterior pituitary.

The association of cleft lip and/or palate with pituitary hormone deficiency has been reported in only 8 patients (Prüsener, 1933; Brewer, 1957; Francés *et al.*, 1966; Zimmerman *et al.*, 1967; Laron *et al.*, 1969; Zuppinger *et al.*, 1971). The pathogenesis of this syndrome has been suggested to stem from the close relationship between midline facial structures and the Rathke's pouch in early fetal development (Tondury, 1976). We report two patients with this rare combination of congenital malformations in whom an evaluation of the hypothalamic-pituitary function was obtained.

## Case reports

**Case 1.** A boy of nonconsanguineous parents of Jewish-Iraqi origin was born with a cleft lip and palate which were surgically corrected in several

stages. Pregnancy was uneventful as was delivery. Birthweight was 4500 g. There were no neonatal complications. During early childhood there were no serious illnesses and mental development was normal but there was, apparently, growth retardation from infancy. At age 7 years secondary hypothyroidism was diagnosed and treatment with thyroid extract was initiated; despite this there was no subsequent improvement in his growth rate.

When referred to our clinic at age 10.2 years he was found to be an alert boy who looked young for his age. He was very short but of proportional build (Table 1), and exhibited several clinical features suggestive of a deficiency of GH and gonadotrophins including acromicria, frontal bossing, overcrowding of teeth, and a small penis (3 × 0.8 cm) (Laron, 1969;

Table 1 Findings in 2 patients with cleft lip palate

	Case 1	Case 2
Chronological age (years)	10.2	21.5
Bone age (years)	4	9
Height (cm)	107.4 (-5 SD)*	136.4 (-5 SD)*
Upper/lower segment ratio	1.15 (normal: 0.9-1.3)†	1.1 (normal: 1.0-1.2)†
Weight (kg)	17.3 (-3 SD)*	33.0 (-4 SD)*
Skinfold (mm)		
Triceps	10	9
Subscapular	10	7
Abdomen	8	9
Head circumference (cm)	49.5 (-2 SD)*	55.7 (-0.5 SD)*
Bicondylar/biparietal ratio	0.6 (normal)‡	0.75 (normal)‡

\*SD height and weight calculated from the 50th centile for age; †Arad and Laron, 1978; ‡Scharf and Laron, 1972.

Abbreviations	
ACTH:	Adrenocorticotrophic hormone
FSH:	Follicle-stimulating hormone
GH:	Growth hormone
ITT:	Insulin tolerance test
LH:	Luteinising hormone
11-OHCS:	11-Hydroxycorticosteroid
T4:	Thyroxine
TRH:	Thyroid-releasing hormone
TSH:	Thyroid-stimulating hormone

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Laron *et al.*, 1977). The testicular volume was 1.5 ml. Neurological examination was unremarkable and in repeated EEGs a slight irregularity was noted on one occasion. X-ray of the sella was normal, with no evidence of intracranial calcifications. Routine chemistry of blood and urine, including specific gravity of urine and osmolality was normal. Fasting blood sugar was repeatedly normal.

The endocrinological evaluation (Table 2) was considered to indicate that the boy had multiple pituitary hormone deficiencies, and lacked GH, TSH, and gonadotrophins, and also, to a partial extent, ACTH. The addition of GH to the thyroxine treatment which he was already receiving elicited an excellent response in linear growth; during the next year he grew 12 cm (Figure). At age 12.5 years there are, as expected, no signs of puberty, and it is planned to administer sex hormones next year.

**Case 2.** A baby boy of consanguineous parents of Jewish-Sephardic origin, was born by breech delivery and suffered neonatal asphyxia, with a birth weight of 3250 g. His cleft lip and palate were corrected in several stages during early childhood. From the beginning his psychomotor development was retarded (IQ 50) and eventually he attended a special school for mental defectives. From infancy he was also noted to be of short stature. Hypopituitarism was suspected at age 6 years but due to neglect by the family it was not until he was 14 years that he received substitution treatment with thyroid extract, but with no improvement in his growth rate.

When referred to our clinic at the age of 21.5 years he was obviously mentally retarded. He was short (Table 1) with several features typical of pituitary hormone insufficiency. He had a short systolic murmur, considered to be functional, and there was

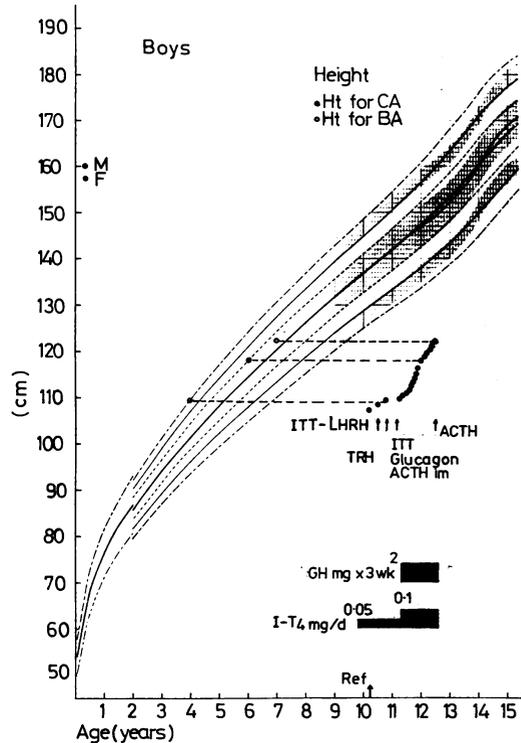


Figure (Case 1). Linear growth during treatment with L-thyroxine alone and combined with GH.

Arrows indicate age at which endocrine tests were performed.

a simian palmar crease on both hands. Routine blood chemistry, specific gravity of urine, and x-ray of the skull and skeleton were normal. The endocrinological evaluation (Table 2) disclosed a deficiency in GH, TSH, ACTH, and gonadotrophins.

Table 2 Endocrinological evaluation of 2 males with cleft lip and palate and hypothalamo-pituitary insufficiency

Hormonal function	Stimulation	Case 1		Case 2	
		Basal	Peak	Basal	Peak
Pituitary	GH (ng/ml)	1.6	2	<1	<1
	IV glucagon	0.5	0.5		
Pituitary-thyroid axis	Prolactin (ng/ml)	8.4	32	11, (47)	47
	T4 (µg/100 ml)	1		1.8	
	TSH (mU/l)	15.4	50	11.2	19.3
Pituitary-adrenal axis	I <sup>131</sup> uptake 2 hours	16%		4.6%	
	24 hours	33%		13%	
	11-OHCS (µg/100 ml)	5	16	4	13
Pituitary-gonadal axis	ACTH 1-24				
	ITT	6.3	6.5	9.7	5.5
	LH (mIU/ml)	0.36	0.74	0.25	0.42
	FSH (mIU/ml)	0.5	0.5	0.5	0.5
Testosterone (ng/100 ml)	—	—	<10		

GH, gonadotrophins, ACTH, and adrenal hormone secretion were measured during L-thyroxine replacement therapy. Conversion: Traditional units to SI—T4: 1 µg/100 ml ≈ 12.87 nmol/l; testosterone: 1 ng/ml ≈ 3.467 nmo/l/l.

## Discussion

In these two patients the deficiency of multiple pituitary hormones (GH, LH, FSH, ACTH, TSH) was clearly proved by the clinical findings and laboratory tests. In Case 1 the normal response of prolactin to TRH is suggestive of damage to the hypothalamic area with the pituitary cells remaining intact. The findings of high basal levels of TSH, despite the inactivity of the thyroid, and the exaggerated response to TRH stimulation are similar to the findings in a group of patients with hypothalamic hypothyroidism described by Illig *et al.* (1975) who explained this phenomenon as resulting from the production of a biologically inactive TSH molecule or end-organ hyposensitivity to TSH. All these observations fit in well with an embryological origin of the syndrome, affecting midline structures in the proximity of the maldeveloped palate, such as Rathke's pouch which migrates distally to develop into the anterior pituitary and connects with the hypothalamus.

In Case 2 additional damage to the pituitary may have been incurred during the breech delivery, with traction of the baby causing partial stalk section. An association between pituitary insufficiency and breech delivery has been noted by others (Rona and Tanner, 1977; Zadik *et al.*, unpublished). Alternatively, the main cause of the mental retardation may have been the asphyxial damage incurred during the baby's delivery. However, minor intellectual deficit has been associated with idiopathic pituitary insufficiency and even with isolated congenital GH deficiency (Frankel and Laron, 1968); this patient was also born of consanguineous parents.

The anterior pituitary insufficiency associated with cleft lip and palate has been found to be of various degrees, depending upon the extent of the teratological lesion. Of the 8 patients previously reported, a complete endocrinological evaluation was carried out only in 4. The single case described by Prüsener (1933) died at 3½ years and necropsy showed compression of the anterior and posterior pituitary by a cyst. In the case described by Brewer (1957), death occurred 4½ hours after birth, and there was aplasia of the pituitary gland. The two patients reported by Francés *et al.* (1966) showed clinical signs suggestive of a selective GH deficiency but no determination of hormone levels was made. The patient reported by Zimmerman *et al.* (1967) had a total lack of gonadotrophins and a partial GH deficiency, although his growth was apparently normal. The patient described by Zuppinger *et al.* (1971) was found to have a defective secretion of both anterior and posterior pituitary hormones, and a coloboma of the right choroid and optic nerve. Of

the two children previously reported from our clinic (Laron *et al.*, 1969), one had essentially no response to stimulation with arginine or insulin-hypoglycaemia, whereas the other gave a normal response to arginine but none to insulin, both having a partial GH deficiency.

There have been reports of syndromes characterised by cleft lip and palate associated with hypospadias and/or cryptorchidism (Christian *et al.*, 1969; Opitz, *et al.* 1969; Abruzzo and Erickson, 1977), but in none of these 3 cases was endocrinological evaluation made, so that the short stature in the case of Abruzzo and Erickson may well have been due to GH deficiency.

The association between cleft lip and palate and a hypothalamic-pituitary insufficiency may be less rare than at present considered. Any child with a cleft lip or palate who also shows slow development, growth retardation, or anomalies of the gonads or genitalia merits comprehensive endocrinological investigation.

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