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The Cohen syndrome: clinical and endocrinological studies of two new cases

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SUMMARY This report concerns two new cases of the Cohen syndrome and gives further information on the variable phenotypical pattern of the disease. The frequency of major and minor clinical signs is reviewed from all the published reports. Among the minor signs we found previously undescribed skeletal abnormalities in one of our patients. The reported delayed onset of puberty, which appears to be a frequent aspect of the syndrome, seems to occur without LH and FSH deficiency, as our patients show.

This syndrome, first reported by Cohen *et al*[1] in three patients in 1973, was confirmed in 1978 by Carey and Bryan[2] who described four new cases.

All the patients had a clinical picture characterised by mild obesity, variable mental retardation, muscle hypotonia, joint hyperextensibility, limb anomalies, and typical craniofacial features.

It has also been confirmed that the syndrome is genetically determined and transmitted as an autosomal recessive trait.[3] This report concerns two additional cases of the Cohen syndrome.

Case reports

CASE 1

He was born on 7.6.76 at term. Delivery was normal and birthweight was 4700 g. He was the fourth child of healthy unrelated parents; the mother was 36 years old and the father 34. Family history was unremarkable and the patient has three normal brothers. The patient was admitted to our hospital at the age of 11 years 9 months because of mental retardation.

Marked muscle hypotonia at birth, psychomotor retardation (spontaneous walking at 2 years, well articulated speech at 3½ years), and a marked weight gain from the age of 5 years were noted.

Physical examination (fig 1) showed a body weight of 39·5 kg (50th to 75th centile), a height of 139 cm (25th to 50th centile), and a head circumference of 50 cm (3rd centile). Also present were truncal obesity, muscle hypotonia, marked joint hyperextensibility, broad and high nasal bridge with

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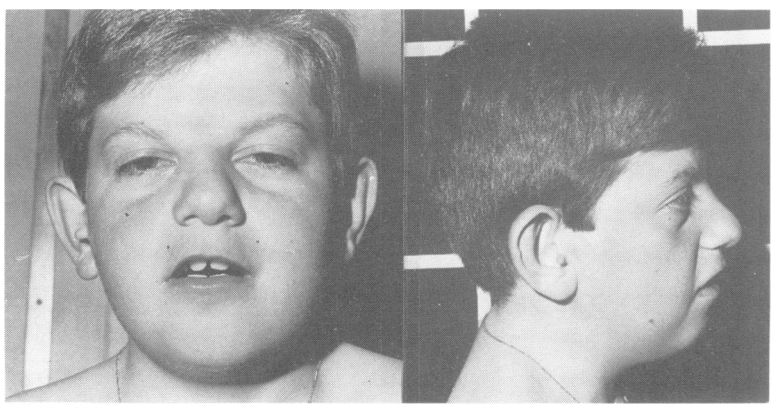

FIG 1 *Facies of patient 1 at 11 years 9 months.*

bulbous tip, narrow palpebral fissures with antimongoloid slants, hypertelorism, protruding ears with auricular tags on the right tragus, open mouth with thin upper lip, large prominent maxillary central incisors, micrognathia, raised shoulders, pectus excavatum, narrow and thin fingers, clinodactyly of fifth fingers, bilateral palmar simian crease, and club feet. Penis length was 5 cm and the testicles, 2 ml in volume, were palpable in the upper part of the inguinal canal. There was no pubic hair.

Routine laboratory examinations including thyroid function, karyotype, fundus oculi, visual acuity, and audiogram were within normal limits. The study of the hypothalamic-pituitary-gonadal function was normal according to the methods previously described[4] (table 1).

IQ measured by WISC was 53, with a verbal performance of 55 to 63. Radiological investigation showed basal kyphosis of the skull with reduction of Lanazertsche's angle (about 90°) and an enlarged sphenoid sinus with abnormal swelling of the tuberculum sellae and lamina quadrilatera. Also present were cleft of posterior arc of C6-7, stocky, flat, and high shoulder blades bilaterally, mild right convex scoliosis of the lumbar tract, and left convex scoliosis of the cervical-dorsal tract. The acetabulum bulged and the pelvis was heart shaped with reduction of the transverse diameter. Bone age was ten years.[3] An intravenous pyelogram was normal.

CASE 2

The parents refused permission to photograph the patient. He was born on 5.7.67, the only child of healthy unrelated parents. The mother was 38 years old and the father 40. The pregnancy was at term with normal delivery, birthweight 3600 g. Bilateral cryptorchidism was present at birth. The family history was negative.

At 10 years 3 months the patient was seen at our out-patient clinic for suspected bilateral cryptorchidism. Strabismus and myopia were present from 2 years of age and marked weight gain with asthenia and muscle hypotonia from 4 years of age were noted. The ERG and VER (visual evoked responses) at 6 years of age showed a deficient photopic function because of a probable congenital dysfunction of the cone system. There was alternating exotropia, bilateral ambliopia, and astigmatism with a visual acuity of 2/10. School performance was poor. Physical examination revealed a body weight of 49·3 kg (>97th centile) and a height of 14·2 cm (75th to 90th centile). There was mild truncal obesity, muscle hypotonia and hyperextensible joints, high and narrow nasal bridge, short philtrum, strabismus,

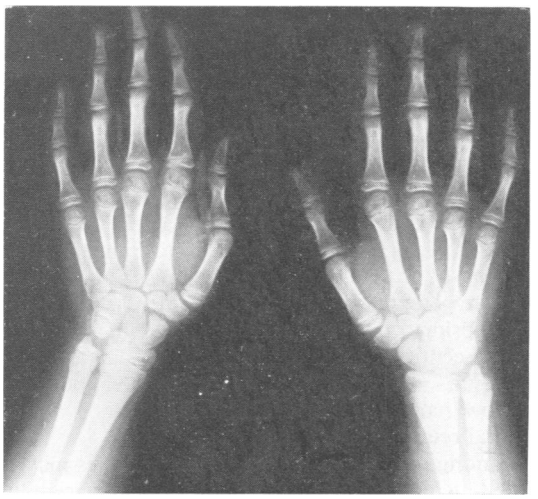

FIG 2 *X-ray of hands of patient 2.*

antimongoloid slants, open mouth with prominent and large maxillary central incisors, narrow highly arched palate and micrognathia, short, narrow hands and feet with thin fingers especially in the distal tract (fig 2), hyperconvex nails, bilateral clinodactyly of the fifth finger, cubitus valgus and genu valgum, penis length of 4 cm, mobile testicles with a volume of 1·5 ml, and absence of pubic hair. At 11 years of age the patient had a weight of 50·8 kg (90th centile), a height of 149 cm (75th to 90th centile), and a bone age of 12½ years. LH and FSH values before and after GNRH stimulation (see table 1) were within normal limits.

TABLE 1 *Endocrinological investigations of the hypothalamic-pituitary-gonadal axis (LH, FSH, and testosterone values, basal and after stimulation with LH-RH and HCG) in the two patients compared with those of normal prepuberal and puberal children*

	LH (mU/ml)		*FSH (mU/ml)*		*Testosterone (ng/100 ml)*	
	Basal	*Peak*	*Basal*	*Peak*	*Basal*	*Peak*
Case 1	5·6	36	6·6	12·5	32	260
Case 2	<1·5	22	2·9	8·5	—	—
Normal prepuberal males	1·78± 0·22*	7·01± 0·85*	1·88± 0·20*	4·72± 0·38*	17·8± 3·6	358± 36·4
Normal puberal males	4·2± 0·49*	36·3± 2·76*	3·3± 0·3*	6·40± 0·6*	—	—

*Mean ± SEM. (To convert testosterone ng/100 ml to nmol/l multiply by 0·03467.)

Discussion

The diagnosis of the Cohen syndrome in our patients emerges from the comparison of their clinical signs with those of the seven cases previously described.[1 2] These are reported in table 2 and allow separation of major signs, occurring with high frequency (from 50 to 100% of cases), and minor signs, occurring less frequently and showing a greater variability.

Major signs are: mild to moderate truncal obesity starting at 3 to 5 years of age, muscle hypotonia, joint hyperextensibility, antimongoloid slants, high nasal bridge, open mouth with prominence of the upper central incisors, high arched palate, short philtrum, micrognathia, maxillary hypoplasia, narrow hands and feet with thin fingers, variable mental retardation, and delayed puberty.

Among the minor signs, ocular anomalies may be noted, which confirm the phenotypical variability of the syndrome suggested by Cohen. In the context of this variability, the presence of previously undescribed skeletal abnormalities in our patient 1 can be explained.

Absent or delayed puberty seems to be a frequent aspect of the Cohen syndrome. In fact, of six patients of puberal age only one had normal puberty. In one case, endocrinological studies showed hypogonadotrophin hypogonadism.[1]

LH and FSH values, basal and after GNRH stimulation, excluded gonadotrophin deficiency in our two prepuberal patients (table 1). In case 1 high peak gonadotrophin values, with respect to chronological and bone age, are difficult to explain for the following reasons. In our experience a normal prepuberal boy aged 11 years can show a puberal gonadotrophin response after GNRH stimulation; in patients with cryptorchidism the gonadotrophin response can be heterogeneous[5 6]; and high peak values can be an early expression of gonadal dysfunction. Autosomal recessive inheritance of the syndrome is claimed on the basis of previous reports on affected sibs in two families. Our two cases do not disagree with this inheritance pattern because case 1 is the only affected among four brothers and case 2 is an only child.

TABLE 2 *Clinical signs of the Cohen syndrome*

	Case 1	*Case 2*	*Other cases*	*Total*
Sex ratio M/F	M	M	4/3	6/3
				(%)
Obesity	+	+	7/7	100
Hypotonia	+	+	7/7	100
Hyperextensible joints	+	+	7/7	100
High nasal bridge	+	+	7/7	100
Open mouth	+	+	7/7	100
High arched palate	+	+	7/7	100
Narrow hands and feet	+	+	7/7	100
Short philtrum	+	+	6/7	89
Micrognathia	+	+	6/7	89
Prominent maxillary central incisors	+	+	6/7	89
Mental retardation	+	+	6/7	89
Cubitus valgus	+	+	6/7	89
Delayed puberty	?	?	4/6	67
Maxillary hypoplasia	+	+	5/7	78
Antimongoloid slant	+	+	5/7	78
Genu valgum	−	+	5/7	67
Strabismus	−	+	4/7	55
Myopia	−	+	4/7	55
Cryptorchidism	+	−	1/4	33
Short stature	−	−	4/7	44
Microcephaly	−	−	4/7	44
Scoliosis	+	−	3/7	44
Mottled retina	−	−	3/7	33
Microphthalmia	−	−	3/7	33
Coloboma	−	−	2/7	22
Finger syndactyly (2nd–3rd)	−	−	2/7	22

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