Intrafamilial variation in Cohen syndrome

I D YOUNG AND J R MOORE

From the Department of Child Health, University of Leicester, Leicester LE2 7LX.

SUMMARY Three sibs with Cohen syndrome are presented. Abnormalities present in all three children include mental retardation, hypotonia, and short philtrum with open mouth and prominent lips. The older two sibs have a similar facies and an engaging personality. The youngest child shows a different facial appearance and marked behavioural problems, thereby illustrating the intrafamilial variability which may occur in this disorder.

The Cohen syndrome¹ is an autosomal recessive disorder characterised by mental retardation, hypotonia, and an apparently typical facies with ocular and oral abnormalities. Several recent papers have reviewed the clinical features of this relatively rare condition, stressing their wide range and variability.²⁻⁵ This report documents three sibs believed to have the Cohen syndrome, who show marked variation in expression of the disorder.

Case reports

The three affected sibs were the only children of healthy unrelated Caucasian parents with no history of relevant hereditary disease on either side of the extended family.

CASE 1

The oldest sib, a boy, was born in 1970 at 36 weeks' gestation after an uneventful, drug free pregnancy. Birth weight was 2.45 kg. There were no problems in the neonatal period other than difficulty with feeding. He first walked at one and a half years and began using sentences at four years. Formal development assessment at the age of seven years yielded an IQ of 58.

This boy had no convulsions or serious illnesses in childhood, his only admission to hospital being for bilateral orchidopexy and circumcision because of a phimosis. He was recorded as being overactive in early childhood, but thereafter was generally well behaved with a kind and affectionate personality.

On examination at the age of 15 years his head circumference (54 cm) fell on the 10th centile, while both height (151 cm) and weight (39 kg) fell below the 3rd centile. His skull showed frontal narrowing and he had an unusual facies (fig 1) with lop ears,

high nasal bridge, flared nares, short philtrum, open mouth, thick protuberant lips, and micrognathia. Examination of his mouth revealed a narrow palate, gingival hypertrophy, large central upper incisors and small lateral upper incisors.

His hands had normal creases with tapering digits which showed nine ulnar loops with a radial loop on the right index finger. There was no evidence of puberty with absent facial and axillary hair. He showed mild generalised joint laxity with hypotonia and normal reflexes. Ophthalmological assessment using mydriasis and slit lamp revealed no abnormality.

Investigations giving normal results included routine haematology and biochemistry, G banded karyotype, blood and urine amino acids, and urinary screen for glycosaminoglycans. Shallow acetabula and a thickened skull vault were noted on skeletal survey. His bone age at a chronological age of 15 years 4 months was 13 years 6 months.

CASE 2

The sister of case 1 was born in 1972 at 37 weeks' gestation with birth weight 2.6 kg. Both the pregnancy and the neonatal period were uneventful. She first walked at 15 months, began using single words at four years, and constructed sentences at seven years. Formal developmental assessment at a chronological age of five years four months yielded a mental age of three years four months.

Other than a single febrile convulsion at the age of nine months, she had no serious illnesses or operations in childhood. Audiology at five years was normal. No behavioural problems were noted in childhood during which she was described as docile, gentle and affectionate.

On examination at the age of 13 years her head circumference (53 cm) and height (153.5 cm) lay on the 25th centile with weight (33 kg) falling below the

Received for publication 17 May 1986.

Accepted for publication 27 June 1986.

FIG 1 AP and lateral views of case 1 aged 15 years.

3rd centile. Her skull showed frontal narrowing and her facies (fig 2) was almost identical to that of her older brother with broad flared nares, short philtrum, open mouth, protruding lips, and micrognathia. She also had a narrow arched palate, gingival hypertrophy, large central upper incisors, and small lateral upper incisors.

General examination (fig 3) revealed a short sternum with breast development consistent with early puberty, a pronounced postural lordosis, and a sacral pit. Her fingers were long and tapering with arches on each except her right thumb which showed an ulnar loop. She had marked joint laxity and mild generalised hypotonia with normal reflexes. Slit lamp examination and fundoscopy were normal.

Investigations giving normal results included routine haematology and biochemistry, blood and urine amino acids, G banded karyotype, and urinary screen for glycosaminoglycans. Shallow acetabula and slight thickening of the skull vault were observed on skeletal survey. Bone age at a chronological age of 13 years 4 months was 12 years.

CASE 3

The youngest sib, a girl, was born in 1975 at 42 weeks' gestation, birth weight 3.01 kg, after an

FIG 2 Facial view of case 2 aged 13 years.

FIG 3 AP and lateral views of case 2 aged 13 years.

uneventful, drug free pregnancy. She had bronchiolitis at seven weeks, from which she made a full recovery, and underwent correction of divergent strabismus at five years of age. Severe constipation was a problem throughout childhood requiring regular treatment with purgatives and enemata.

She first sat unsupported at 15 months but did not walk unassisted until eight years and when last assessed at the age of 10 years she had developed no meaningful speech. Behaviour during infancy was normal but by the age of three years she was noted to be unhappy, restless, and aggressive with frequent temper tantrums, characteristics which persisted throughout childhood. Unlike her older sibs she was never affectionate or loving. Developmentally she showed no evidence of regression and never had any convulsions. Hearing assessment at the age of five years was normal.

Examination at the age of 10 years revealed an agitated, restless child with head circumference (48.5 cm) and height (119.6 cm) both falling below the 3rd centile and weight (23.2 kg) lying on the 3rd centile. She had a prominent forehead and rounded face (fig 4) with a flat, broad nasal bridge, antverted, flared nares, short philtrum, and thick lips. Her interpupillary distance was 5.75 cm (between

FIG 4 Facial view of case 3 aged 10 years.

the 75th and 97th centiles). Her palate and gums were normal and she had not lost any of her primary dentition which was also normal.

General examination (fig 5) revealed mild truncal obesity, mild generalised hypotonia, no excess joint laxity, and normal reflexes. Her palmar creases were normal and she had short tapering fingers with arches on the index fingers and ulnar loops on the remaining digits.

Visual assessment confirmed her to be visually alert with full ocular movements and a residual alternating divergent strabismus. She had a moderate degree of hypermetropic astigmatism. The right fundus was normal but the left showed a small area of depigmentation at the left macula.

Routine haematology and biochemistry, thyroid function tests, blood and urine amino acids, G banded karyotype, and urinary screen for glycosaminoglycans were normal. Skeletal survey showed shallow acetabula and abnormal modelling of the phalanges and metacarpals. A thoracic scoliosis was also noted. The bone age was seven years ten months at a chronological age of 10 years one month.

Examination of both parents, including G banded karyotype, revealed no abnormality. A maternal Guthrie test was normal.

FIG 5 Case 3 aged 10 years.

Discussion

These children have presented a considerable diagnostic problem. Firstly, the question arises of whether they all have the same disorder. Careful chromosome studies in the family have failed to show any suggestion that the children have different unbalanced karyotypes resulting from segregation of a balanced arrangement in one or other parent. The two older sibs have an almost identical phenotype with similar facies, joint laxity, and pleasing disposition. In contrast, the younger sib shows more severe developmental delay in association with difficult behaviour and a somewhat different facial appearance.

However, review of the clinical features, as listed in the table, indicates that all three children share a number of findings in common, including short philtrum, open mouth, hypotonia, and delayed bone age, so that it seems reasonable to accept that they are likely to have the same disorder.

Several diagnoses have been entertained in these patients. The combination of developmental delay, bulbous nose with thick nasal alae, ligamentous laxity, and tapering fingers in the oldest patient prompted the diagnosis of the Coffin-Lowry syndrome. However, the arrival of two affected sisters, one with more severe manifestations, was not consistent with the X linked semidominant mode of inheritance ascribed to the Coffin-Lowry syndrome.⁶ On the basis of frontal narrowing, gingival hypertrophy, and cryptorchidism, the Smith-Lemli-Opitz

TABLE Clinical features in cases 1 to 3.

	Case 1	Case 2	Case 3	Cohen syndrome ²⁻⁵ (%)
Developmental delay	+	+	+	97
Short stature	+	-	+	68
Microcephaly	-	-	+	52
Frontal narrowing	+	+	-	
Lop ears	+	+/-	-	
High nasal bridge	+	+	-	92
Flared nares	+	+	+	
Short philtrum	+	+	+	84
Protuberant lips	+	+	+	
Open mouth	+	+	+/-	83
Gingival hypertrophy	+	+	-	
Large central incisors	+	+	?	70
Micrognathia	+	+	-	87
Tapering fingers	+	+	+	89
Truncal obesity	-	-	+	
Lordosis	-	+	-	38
Scoliosis	-	-	+	38
Joint laxity	+	+	-	54
Hypotonia	+	+	+	92
Strabismus	-	-	+	52
Shallow acetabula	+	+	+	
Delayed bone age	+	+	+	75
Delayed puberty	+	-	?	83

syndrome was also considered, but in retrospect none of the children shows the typical facies or dermatoglyphs of this condition.

Review of the table shows the considerable overlap of clinical features shared by these children and reported cases of the Cohen syndrome. All show developmental delay with hypotonia, a similar circumoral appearance, tapering fingers, and delayed bone age. The older two sibs have large central incisors typical of the Cohen syndrome, while the youngest shows delayed loss of the primary dentition which is otherwise normal. Other findings in cases 1 and 2 which have been noted in the Cohen syndrome include gingival hyperplasia,⁷ large prominent ears,^{2 4 8} narrow frontal diameter,⁸ and cheerful disposition.^{3 9}

Neither of the two older children has any of the ocular stigmata of this disorder, but case 3 shows strabismus with hypermetropia and astigmatism, which has been documented in the Cohen syndrome,⁷ along with an area of depigmentation in the left macula. Case 3 also had cold, cyanosed extremities on one of the three occasions on which she was examined, an observation noted by others.² No record of shallow acetabula has been traced in other reports, although Balestrazzi *et al*¹⁰ described an affected child with a bulging acetabulum.

Goecke *et al*⁷ have commented upon the variability of the Cohen syndrome and how this may render difficult the diagnosis of an isolated case. They also make the point that many of the cardinal signs and symptoms in Cohen's original patients may be absent. The family now reported further illustrates this variability of features of the Cohen syndrome, not only between families but within a sibship. For once, genetic heterogeneity may not be the rule.

The authors are grateful to Dr D P Duckett for the cytogenetic studies, Mr A R Fielder for ophthalmological assessments, Dr A C Lamont for review of the radiographs, and Mrs Penny Marston for typing the manuscript.

References

- ¹ Cohen MM, Hall BD, Smith DW, Graham CB, Lampert KJ. A new syndrome with hypotonia, obesity, mental deficiency and facial, oral, ocular and limb anomalies. *J Pediatr* 1973;**83**:280-4.
- ² Friedman E, Sack J. The Cohen syndrome: report of five new cases and a review of the literature. *J Cran Genet Dev Biol* 1982;**2**:193-200.
- ³ Norio R, Raitta C, Lindahl E. Further delineation of the Cohen syndrome; report on chorioretinal dystrophy, leukopenia and consanguinity. *Clin Genet* 1984;**25**:1-14.
- ⁴ North C, Patton MA, Baraitser M, Winter RM. The clinical features of the Cohen syndrome: further case reports. *J Med Genet* 1985;**22**:131-4.
- ⁵ Resnick K, Zuckerman J, Cotlier E. Cohen syndrome with bull's eye macular lesion. *Ophthalmic Paediatr Genet* 1986;**7**:1-8.
- ⁶ Hunter AGW, Partington MW, Evans JA. The Coffin-Lowry syndrome. Experience from four centres. *Clin Genet* 1982;**21**:321-35.
- ⁷ Goecke T, Majewski F, Kauther KD, Sterzel U. Mental retardation, hypotonia, obesity, ocular, facial, dental and limb abnormalities (Cohen syndrome). *Eur J Pediatr* 1982;**138**:338-40.
- ⁸ Kousseff BG. Cohen syndrome: further delineation and inheritance. *Am J Med Genet* 1981;**9**:25-30.
- ⁹ Fryne JP, Van Den Berghe H. The Cohen syndrome. *J Genet Hum* 1981;**29**:449-53.
- ¹⁰ Balestrazzi P, Corini L, Villani G, Bolla MP, Casa F, Bernasconi S. The Cohen syndrome: clinical and endocrinological studies of two new cases. *J Med Genet* 1980;**17**:430-2.

Correspondence and requests for reprints to Dr I D Young, Department of Child Health, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX.