

The acrocallosal syndrome in first cousins: widening of the spectrum of clinical features and further support for autosomal recessive inheritance

ALBERT SCHINZEL

From the Department of Medical Genetics, University of Zürich, Switzerland.

SUMMARY First cousins, related through their mothers, showed a pattern of craniofacial, brain, and limb anomalies consistent with the acrocallosal syndrome. Both patients had a defect of the corpus callosum, macrocephaly with a protruding forehead and occiput, hypertelorism, non-horizontal palpebral fissures, a small nose, notched ear lobes, and postaxial polydactyly of the hands. The boy, in addition, had hypospadias, cryptorchidism, inguinal hernias, duplication with syndactyly of the phalanges of the big toe, and a bipartite right clavicle. The girl had an arachnoidal cyst, a calvarian defect, and digitalisation of the thumbs. Motor and mental development was retarded in both patients. This observation provides further evidence of probable autosomal recessive inheritance of the acrocallosal syndrome and widens the spectrum of clinical findings and the variability of features in this rare malformation syndrome.

There are currently eight published reports of the acrocallosal syndrome (ACS),¹⁻⁵ first described in 1979,⁶ and another dozen cases known by personal communication. The patients were classified as representing the syndrome by a characteristic combination of congenital anomalies, particularly craniofacial dysmorphism, agenesis or hypoplasia of the corpus callosum, duplication of the phalanges of the big toe (and, more rarely, the thumb), and postaxial polydactyly of the fingers or toes or both. As is usual in most malformation syndromes, phenotypic variability became evident after a few patients were studied, mainly concerning the presence of rarer additional malformations including cleft lip/palate,^{2,5} high degree polydactyly,³ the presence and extent of syndactyly between various fingers and toes, and other brain malformations in combination with agenesis of the corpus callosum.⁵ The first pair of affected sibs were discordant for cleft palate and a cyst in the brain.⁵

The present paper reports first cousins concordant for deficiency of the corpus callosum, craniofacial anomalies, and postaxial polydactyly of the fingers, but discordant for duplication of the big toes. The boy is the first patient with ACS to have hypospadias. The patients represent the second instance of occurrence of the acrocallosal syndrome in more than one member of a family and lend further

support to autosomal recessive inheritance of this syndrome. In addition, they demonstrate the phenotypic variability in the acrocallosal syndrome.

Case reports

The pedigree is shown in fig 1. The family of II.3 and II.8 originates from the Appenzell, north-eastern Switzerland. II.2 originates from the Kanton of St Gallen, from an area close to the Appenzell; however, consanguinity could not be proven. II.7 is an adopted child whose parents are unknown.

PATIENT 1 (III.8)

Both parents were born in 1954, and two healthy

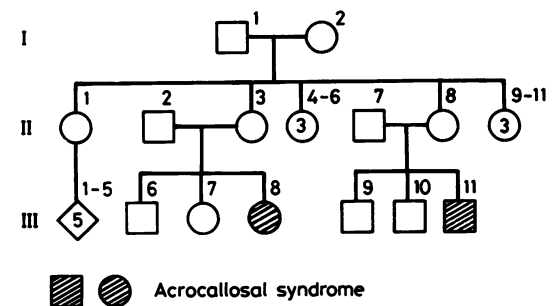


FIG 1 Pedigree of the two patients. Patient 1, III.8; patient 2, III.11.

Received for publication 24 April 1987.
Revised version accepted for publication 1 June 1987.

and normal sibs were born to the couple in 1978 (birth weight 3560 g) and 1980 (birth weight 3770 g). Patient 1, a girl, was the product of the third pregnancy. She was born at term in 1982 after an uneventful pregnancy. Apgar scores were 6, 6, and 8 after one, five, and 10 minutes, respectively. At birth, weight was 3550 g (50th to 90th centile), length 52 cm (90th centile), and head circumference 38 cm (above the 97th centile). A large, unusually shaped head with a large anterior fontanelle and postaxial polydactyly of both hands were noticed. She first smiled at four months, sat unsupported at 16 months, and walked with support at three years and alone at four years of age.

Progressive scaphocephaly was of major concern to the parents and physicians and prompted coronal craniectomy at four months, which, however, did not lead to improvement of the skull configuration. At the same time, the supernumerary fingers were also removed. The skull growth curve paralleled the 97th centile at about + 3 SD above the mean (head circumference 51 cm at 18 months, 52 cm at 25 months, 54.1 cm at four years two months of age).

On detailed clinical examination at 18 months of age (figs 2 and 3, table), length was 78 cm (about the 3rd centile) and weight was 10.7 kg (25th to 50th centile). The patient presented as a hypotonic and

severely mentally retarded girl with a disproportionately large and unusually shaped skull and thoracic kyphosis. She had brachycephaly, a large and prominent forehead, a narrow biparietal diameter, ocular hypertelorism (inner canthal distance 32 cm=above the 97th centile), flaring of the medial eyebrows, upward slanting palpebral fissures, a short nose with a broad bridge, a short upper lip, down turned corners of the mouth, receding mandible, a normal palate without a bifid uvula, and low set ears with hypoplastic, notched lobules. She also had diastasis recti, normal female genitalia, finger-like and hyperextensible thumbs which could not be opposed, scars on the lateral sides of the little fingers from surgery to remove the sixth rays, genua recurvata, and feet in a drop foot position. Muscle tone was increased in the lower limbs and decreased elsewhere.

X rays, in addition, showed an osseous defect in the right parieto-occipital area of the skull and bilateral hip dislocation. Bilateral osteotomy was performed at four years four months. Cranial computed tomography performed at 18 months disclosed severe hypoplasia (almost absence) of the corpus callosum, a large, asymmetrical cisterna magna, an arachnoidal cyst, and defective ossification of the right parasagittal parieto-occipital area of

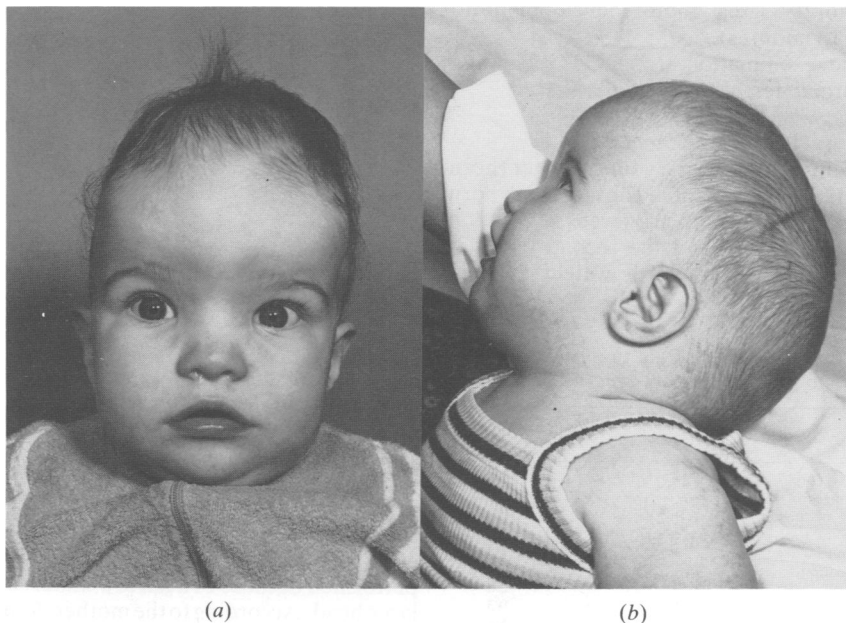


FIG 2 Head of patient 1 at (a) 11 months and (b) six months of age. Note large, prominent forehead, hypertelorism, upward slanting palpebral fissures, flaring of medial eyebrows, low set ears with small lobules containing two notches, short neck, scar from coronal craniectomy, and flat occiput

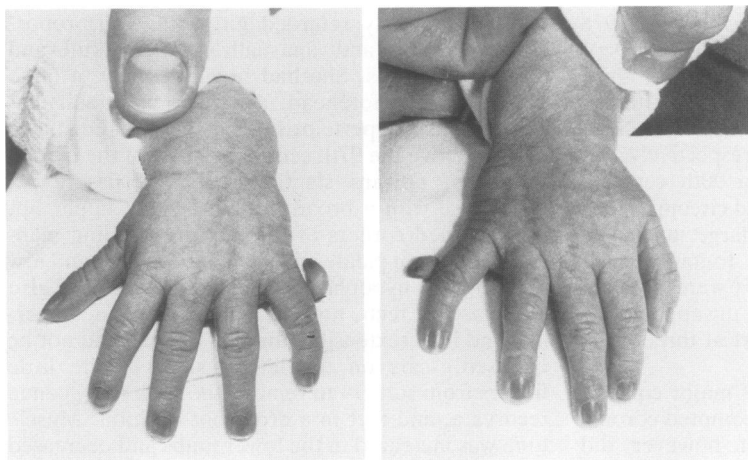


FIG 3 Hands of patient 1 at five days of age. Note bilateral postaxial polydactyly and clinodactyly of little fingers and finger-like thumbs.

the skull. Ophthalmological examination at four years of age was normal. At 17 months, psychological testing revealed a gross motor development consistent with an age of three to four months, fine motor skills, language, and social behaviour consistent with six to seven months, and a total developmental quotient of 50. At 38 months of age, her developmental age, according to a Denver test, was 14 to 16 months with marked dissociation (language at about 10 months, gross motor development 16 months, play 18 months).

Chromosome examination using GTG banding revealed a normal female karyotype.

PATIENT 2 (III.11)

The mother of this boy (II.8) is a younger sister (born in 1959) of the mother of patient 1. The father was born in 1958. The first son was born at 36 weeks' gestation with a weight of 1890 g, and the second boy was born in 1983 at 38 weeks, birth weight 2300 g.



FIG 4 Patient 2 at six months. Note large and prominent forehead, ocular hypertelorism, downward slanting palpebral fissures, hypoplasia of upper and lower lids, and notches in left earlobe.

TABLE Major clinical features of the two patients in this report compared to eight previously reported cases.

| Clinical features | Patient 1 | Patient 2 | Refs 1-5 (n=8) |
|--|-----------|-----------|----------------|
| Hypoplastic or absent corpus callosum | + | + | 7/7 |
| Duplication of phalanges of big toe | - | + | 7/8 |
| Postaxial polydactyly of fingers | + | + | 7/8 |
| Postaxial polydactyly of toes | - | - | 6/8 |
| Craniofacial dysmorphism (see text) | + | + | 8/8 |
| Severe mental retardation (see text) | + | + | 8/8 |
| Cleft lip/palate | - | - | 2/8 |
| Hypospadias in males | 0 | + | 0/3 |
| Inguinal hernias | - | + | 5/8 |
| Cryptorchidism | 0 | + | 0/3 |
| Syndactyly of toes (excluding additional ones) | - | - | 4/8 |

The proband was born in 1985 at 36 weeks' gestation after a normal pregnancy; caesarean section was performed because of a narrow maternal pelvis and a large head. According to the mother, fetal movements were less vigorous than in the two previous pregnancies. Birth weight was 2570 g (50th centile), length 45 cm (25th to 50th centile), and head



FIG 5 Radiographs of the feet of patient 2 at four months of age. Note bifid metacarpal and duplication of phalanges of big toes.



FIG 6 Radiographs of the hands of patient 2 at four months. Note bilateral postaxial polydactyly with bifid fifth metacarpal on the right hand.

circumference 34 cm (90th centile). Apgar scores were 9, 10, and 10 at one, five, and 10 minutes, respectively. An unusual skull configuration, hexadactyly, and hypospadias were noticed at birth. Both feet had duplication of the big toes with complete syndactyly. The hands showed bilateral postaxial polydactyly with fully formed nails, the right additional finger being distinctly longer than the left and containing three phalanges.

The baby fed poorly. Motor development was retarded from the beginning. At four months he was operated upon for bilateral inguinal hernias, a right

undescended testis, preaxial polydactyly of the feet, and postaxial polydactyly of the hands and feet.

Clinical examination at six months of age (table, fig 4) showed a retarded boy with multiple minor anomalies. Length (65 cm) was on the 25th centile, weight (7.48 kg) 50th centile, and head circumference (44.2 cm) 50th to 75th centile. The head was large, broad, and brachycephalic with a mildly prominent forehead, high anterior hairline, and a large (5×6 cm) anterior fontanelle. There was hypertelorism (ICD=3.5 cm, above the 97th centile), downward slanting palpebral fissures, alternat-

ing convergent strabismus, inner epicanthic folds, sparse eyebrows, hypoplasia of the upper lids, absent lower lids, a lid length of 2.2 cm (normal), a short nose (length 2.8 cm), and normally positioned ears of normal morphology except for bilateral lobular notches. Nipples were widely spaced. Further findings included bilateral scars from herniotomy, hypospadias with the opening in the sulcus coronarius, an approximately 20° clockwise rotation of the penis, tapering fingers, narrow finger nails and toenails, and scars from operations to remove the additional fingers and toes.

Radiographs at four months (figs 5 and 6) confirmed postaxial polydactyly of the upper extremities, duplication with partial syndactyly of both halluces, and a right bipartite clavicle. Cranial sonography showed lateralisation of the lateral ventricles and a third ventricle extending unusually high cranially, both suggestive of agenesis or severe hypoplasia of the corpus callosum.

The baby smiled, but he did not fix or follow objects with his eyes and did not respond to his mother or to other optic stimuli; however, he apparently responded to acoustic stimuli. He did not grasp or reach for objects and did not turn over. His motor development at six months corresponded to that of a two month old child.

The karyotype from GTG banded preparations was normal, 46,XY.

Discussion

The two patients in this report increase the number of reported patients with the acrocallosal syndrome to 10 and the instances of more than one affected patient in a family to two.⁵ The first report of familial occurrence of the acrocallosal syndrome concerned sisters, but in the present family, first cousins of different sex, related through their mothers, were observed. Although the evidence is less strong than in the case of affected sibs, the most likely explanation in the absence of a chromosome aberration is still autosomal recessive inheritance with the implication that both fathers are, by chance, also heterozygotes. The father of patient 1 originates from the same area as his wife, while we have no data on the origin of the family of the husband of her sister. It is noteworthy that not only two of the three families of the cousins in this report, but also both parents of the sibs reported by Schinzel and Kaufman,⁵ and both parents of case 2 of Schinzel and Schmid,¹ originate from this small

area in north-eastern Switzerland. This might be due to chance, but it might also indicate a higher frequency of the gene in this area.

The present observations allow a better insight into the variability of abnormalities caused by homozygosity for the same mutant gene. For example, patient 1 of this report is the first reported case of the acrocallosal syndrome with normal big toes, and patient 2 is the only one out of four males with hypospadias. Since postaxial polydactyly is also quite variable, it is likely that patients affected with the ACS will exist who lack any kind of hexadactyly. For a classification of further cases, it is therefore important to consider the syndrome in patients with the characteristic craniofacial and brain findings and development as well as rarer associated findings. Once again, the name initially given (acrocallosal syndrome) might not be correct either concerning the acro part or, as shown from case 1 of Nelson and Thomson,² the callosal part. In fact, the author has observed two similar cases with neither pre-/postaxial hexadactyly nor syndactyly, but with agenesis of the corpus callosum, strikingly similar craniofacial and other features, and a similar degree of mental retardation to that observed in all previous cases.

We wish to thank Drs Christoph Francke (Utzwil), Remo Largo (Zürich), and R Leuthardt (St Gallen) for referring the patients to us.

References

- Schinzel A, Schmid W. Hallux duplication, postaxial polydactyly, absence of the corpus callosum, severe mental retardation, and additional anomalies in two unrelated patients: a new syndrome. *Am J Med Genet* 1980;6:241-9.
- Nelson MM, Thomson AJ. The acrocallosal syndrome. *Am J Med Genet* 1982;12:195-9.
- Sanchis A, Cervero L, Martinez A, Valverde C. Duplication of hands and feet, multiple joint dislocations, absence of corpus callosum and hypsarrhythmia: acrocallosal syndrome? *Am J Med Genet* 1985;20:123-30.
- Legius E, Fryns JP, Casaer P, Boel M, Eggermont E. Schinzel acrocallosal syndrome: a variant example of the Greig syndrome? *Ann Genet (Paris)* 1985;28:239-40.
- Schinzel A, Kaufmann U. The acrocallosal syndrome in sisters. *Clin Genet* 1986;30:399-405.
- Schinzel A. Postaxial polydactyly, hallux duplication, absence of the corpus callosum, macrocephaly and severe mental retardation: a new syndrome? *Helv Paediatr Acta* 1979;34:141-6.

Correspondence and requests for reprints to Professor A Schinzel, Institute of Medical Genetics, University of Zürich, Raemistrasse 74, CH-8001 Zürich, Switzerland.