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Three sibs with phalangeal anomalies, microcephaly, severe mental retardation, and neurological abnormalities

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Abstract

This paper describes three children of a Pakistani first cousin marriage with a distinctive, non-progressive disorder characterised by variable phalangeal anomalies, microcephaly, pre- and postnatal growth retardation, poor vision, dystonic movements, a characteristic face, and severe mental retardation. This combination of features seems to be distinct and to represent a new autosomal recessive syndrome.

This paper describes three mentally retarded, dysmorphic children of a consanguineous Pakistani couple. The disorder appears distinctive and we can find no previous similar reports.

Case reports

The parents are Pakistani Muslim first cousins. They have three affected children, two girls aged 10 and 8 years and a boy of 2 years. They also have two normal boys aged 9 and 7 years and have had three first trimester miscarriages. No other similarly affected children were known of in the extended family where there have been other consanguineous matings. The parents and their two other children were healthy, well grown, of normal intelligence, and had no dysmorphic features. Parental chromosomes were examined on two occasions and found to be normal.

CASE 1

A female child was born at term by forceps after an unremarkable pregnancy. Complete cutaneous syndactyly of the third and fourth digits was noted. Head circumference, length, and weight measurements were on the 3rd centile. By 6 months the child had developed a characteristic face different from others in the family and was noted to have delayed milestones, hypotonia, and hyperreflexia.

A murmur was also discovered during the first year of life, which on investigation was found to be a ventricular septal defect; this was not symptomatic. During the second year a venous varix developed behind the right eye, causing proptosis and occasional subluxation of the eye. This grew alarmingly for four years and then partially regressed. During ophthalmic examination she was found to have bilateral optic atrophy, but had some remaining vision.

The girl was 10 years old when seen. She was severely mentally retarded, not moving independently, making no vocalisations, and being totally dependent for feeding and toileting. Development seemed static at about the 3 month level. On examination she had a broad, hairy forehead, a broad nasal bridge and prominent columella, hypoplastic alae nasi, short philtrum, and a straight mouth with thin lips. The palpebral fissures were downward slanting (fig 1). There was complete cutaneous syndactyly of the third and fourth digits and a broad nail on the fourth digit (fig 2). Elbow extension was restricted by 30° and there were bilateral single palmar creases. The fifth toe showed brachyclinodactyly with nail hypoplasia (fig 3). An accessory nipple was present

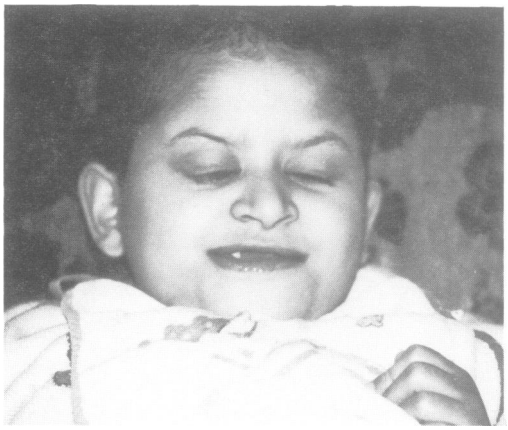

Figure 1 Face of case 1.

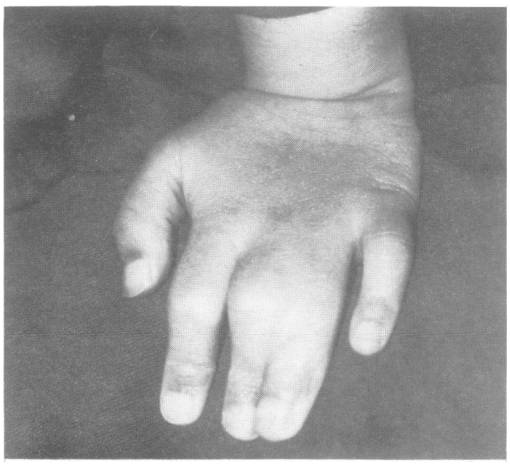

Figure 2 Hand of case 1.

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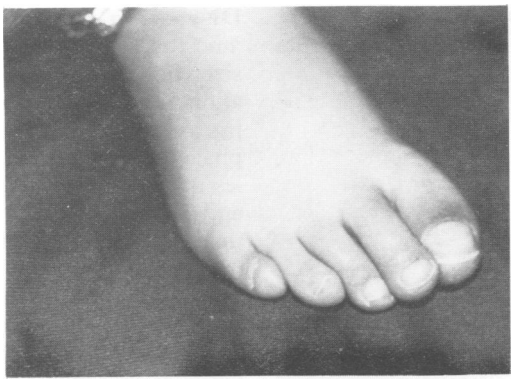

Figure 3 Foot of case 1.

bilaterally on the subcostal margins. The ventricular septal defect murmur was still present, but the defect was asymptomatic.

She had moderately severe spastic/dystonic paraplegia, with brisk reflexes and ankle clonus. There were no contractures. The tongue showed occasional odd movements, comprising a slow, steady protrusion of the tongue to reach about 5 cm in length, occurring over 30 seconds. This probable dystonic movement did not appear to cause distress nor to occur to any particular stimulus. The tongue was of normal size between excursions. Head circumference, weight, and height were less than the 3rd centile for age.

The following investigations were performed and found to be normal: cytogenetic analysis, full blood count with microscopy of white cells, serum Na, K, Cl, Ca, creatinine, acid base, liver function, amino and organic acids, pyruvate, lactate, and ammonia. A cranial ultrasound scan at 6 months was normal but other cerebral imaging was not performed. A skeletal survey at 10 years showed some flattening of the occipital vault, but no other skull anomalies. The proximal epiphysis of the distal phalanx was larger than usual in all toes and there was a recurvatum deformity in the lateral three (fig 4). The terminal phalanx of the fourth digit was duplicated. The humerus, radius, ulna, spine, hips, and pelvis were normal.

CASE 2

Pregnancy and delivery were uneventful. At birth bilateral cutaneous syndactyly of the third and fourth digits was noted, as well as head circumference, length, and weight measurements about the 3rd centile. By 3 months the child looked like her affected older sister. Soon after it became clear that this second child was also developmentally delayed, hypotonic, and hyperreflexic.

When seen at 8 years of age she was severely mentally retarded and, as in her sister, development seemed static from 3 months. On examination her face was similar to her sister's (fig 5). She had complete and bilateral cutaneous third and fourth digit syndactyly and a single palmar crease on the left hand. Elbow extension was restricted bilaterally by 30°. Fifth toe brachyclinodactyly and nail hypoplasia were also present. Ophthalmic examination showed optic atrophy with some remaining useful vision. She also had a moderately severe spastic/dystonic paraplegia and exhibited paroxysmal slow tongue extension. Head circumference, weight, and height were less than the 3rd centile for age.

Cytogenetic analysis was normal.

CASE 3

A boy was born after an uneventful pregnancy and delivery. He was noted to have bilateral single palmar creases and bilateral limited elbow extension, but he did not have digital syndactyly. By 3 months he too was developing a face characteristic of his affected sibs and was noted to be developmentally delayed.

When seen at the age of 2 years, he was severely developmentally delayed, hypotonic, and hyperreflexic. On examination his facial features were as in his affected sisters (fig 6). As well as the upper limb anomalies previously noted, he had fifth toe brachyclinodactyly and nail hypoplasia. He had occasional tonic epileptic fits and was well controlled on carbamazepine. He also exhibited the tongue extension of his affected sibs and his head circumference,

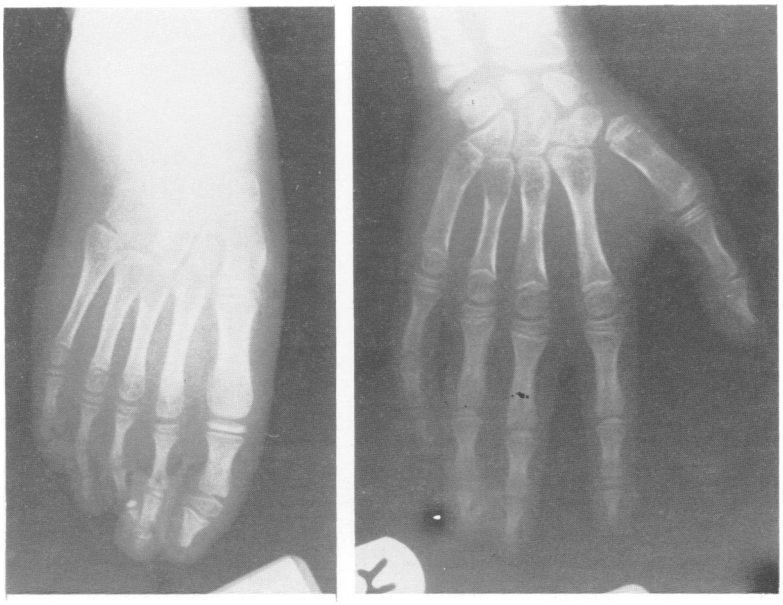

Figure 4 Radiographs of hand and foot of case 1.

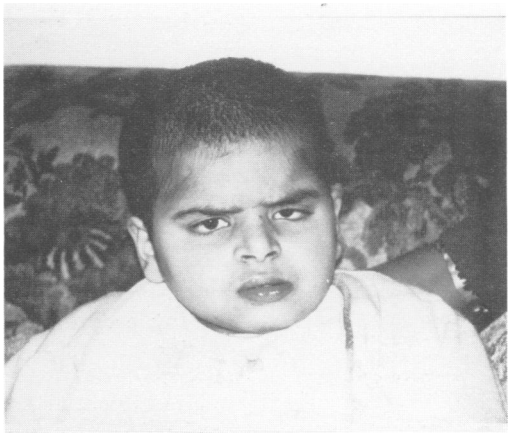

Figure 5 Face of case 2.

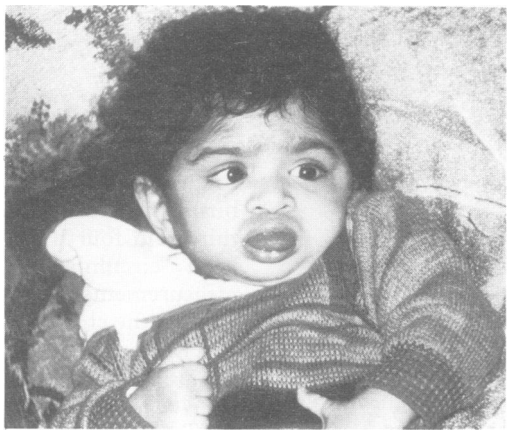

Figure 6 Face of case 3.

height, and weight were on, or less than, the 3rd centile for his age.

Case 3 has not had detailed fundoscopic examination. Cytogenetic analysis showed a pericentric inversion of chromosome 9.

The clinical features of the affected children are summarised in the table.

Clinical features of the study cases.

	Case 1	Case 2	Case 3
Age when seen	10y	8y	2y
Height centile	<3rd	<3rd	<3rd
Weight centile	<3rd	<3rd	<3rd
Head circumference centile	<3rd	3rd	3rd
Narrow, tall toes	+	+	+
Brachyclinodactyly of 5th toes	+	+	+
Hypoplasia of 5th toenail	+	+	+
Finger 3/4 syndactyly	R	R+L	–
Single palmar creases	R+L	L	R+L
Restricted elbow extension	+	+	+
Mild spastic/dystonic paraplegia	+	+	+
Dystonic tongue movements	+	+	+
Eye venous varix	+	–	–
Bilateral accessory nipples	+	–	–
Congenital heart anomaly (VSD)	+	–	–
Optic atrophy with some vision	+	+	?

Discussion

The three children described are all of small size with microcephaly, severe mental retardation, mild spastic/dystonic paraplegia, tongue protrusion, a characteristic face, and variable phalangeal anomalies. The phalangeal anomalies involve epiphyses, phalangeal duplication, and type 1 syndactyly, so showing variable defects in phalangeal formation and secondary modelling. There is no suggestion as to the underlying cause of this condition. As to the inheritance, while a microdeletion cannot be excluded, normal parental chromosomes and parental consanguinity suggest that autosomal recessive inheritance is likely. Although only seen in case 1, the accessory nipples, ophthalmic venous varix, and heart malformation are presumed to be part of the condition. Cranial imaging of at least one of the sibs would have been desirable to delineate the neurological pattern further, but it was not felt justified on medical grounds.

The London Dysmorphology Database[1] lists 13 autosomal recessive conditions with both syndactyly and mental retardation as a feature. Of these, 12 could be dismissed; five involved cleft lip and palate, three are acrocephalosyndactyly syndromes, two involve anophthalmos or cryptophthalmos, one retinal dystrophy, and one obesity and radial aplasia. The remaining condition was described by Filippi.[2] He described an Italian family where three of eight children had severe mental retardation, 3/4 finger and 2/3/4 toe syndactyly, growth retardation, and a characteristic face. Although the families have several overlapping major features, we feel the conditions are distinct, as the facial appearances were different and the children in the Filippi report did not have localising neurological signs.

1 Baraitser M, Winter R. *The London Dysmorphology Database.* Oxford: Oxford University Press, computer edition, 1991.
2 Filippi G. Unusual facial appearance, microcephaly, growth retardation and syndactyly. A new syndrome. *Am J Med Genet* 1985;22:821–4.