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ORIGINAL ARTICLE

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New dominant syndrome of microcephaly, facial abnormalities, micromelia, and mental retardation

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Abstract We report on three brothers, aged 6, 3, and 2 years, with a hitherto undescribed combination of microcephaly, facial abnormalities, micromelia, and mild mental retardation. Their facial abnormalities included a forehead with bitemporal constriction, upslanting palpebral fissures, synophrys, a short nose with anteverted nostrils, a short columella, a cupid bow-shaped, thin vermilion border of the upper lip, and micrognathia. Their mother had similar clinical manifestations, but was of normal intelligence. The disease was apparently transmitted in a dominant fashion.

Key words Dominant inheritance · Facial abnormality · Mental retardation · Microcephaly · Micromelia

Introduction

We report on three brothers and their mother with similar clinical features who may represent an undescribed condition.

Clinical reports

The clinical findings in the three brothers and their mother are summarized in Tables 1 and 2, and Figs 1 and 2, and their pedigree is shown in Fig. 3.

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Patient 1 (III-11)

The propositus, a 6-year-old boy, was born after a 41-week pregnancy to a non-consanguineous 30-year-old, primigravid mother and a 31-year-old father. There was no history of viral illness, X-ray exposure, or medication during the pregnancy. His birth weight was 2650 g (−1.6 SD), length 48 cm (−1.0 SD), and head circumference 33 cm (−0.3 SD). He suffered from recurrent respiratory infections in early infancy. A right inguinal hernia was surgically repaired at age 2.5 years.

When seen at age 6 years, he weighed 13.8 kg (−2.4 SD), measured 103.8 cm (−1.7 SD) in length, and had a head circumference of 46.2 cm (−2.9 SD). His arm span was 102.2 cm. He had a narrow bifrontal diameter of 10.7 cm. He had upslanting palpebral fissures, synophrys, hyperopia, a short nose with anteverted nostrils and a short columella, a cupid bow-shaped, thin vermilion border of the upper lip, and micrognathia (Fig. 1a). His hands were small with short fifth fingers. His intelligence quotient (IQ) was 71. He was hyperactive and had a short attention span.

The plasma growth hormone level was normal. The plasma and urinary amino acid values were within the normal limits. High-resolution, G-banded chromosome analysis was normal.

Patient 2 (III-12) and *patient 3* (III-13)

Patients 2 and 3, now 3 years 8 months and 2 years, respectively, are younger brothers of patient 1. Their clinical findings are nearly identical to those of patient 1, and are summarized in Tables 1 and 2, and presented in Fig. 1 (b and c).

Mother (II-8)

When the woman who became the mother of the three patients was born, her mother and father were both 36 years old. Her birth weight was reported to be low.

Table 1 Clinical data of patients 1–3 and their mother

Clinical findings	Patient 1 (III-11)	Patient 2 (III-12)	Patient 3 (III-13)	Mother (II-8)
Age (years)	6 3/12	3 8/12	2	36
Sex	M	M	M	F
Maternal age at birth (years)	30	33	34	36
Paternal age at birth (years)	31	34	35	36
Gestational age (weeks)	41	39	39	?
Birth weight (g) (SD)	2650 (−1.7)	2550 (−1.7)	2810 (−1.0)	?
Birth length (cm) (SD)	48.0 (−1.1)	46.0 (−2.0)	48.5 (−0.6)	?
Weight (kg) (SD)	13.8 (−2.4)	11.0 (−2.5)	8.7 (−2.8)	47.0 (−0.8)
Height (cm) (SD)	103.8 (−1.7)	89.4 (−2.0)	78.0 (−2.8)	146.0 (−2.1)
Span length (cm)	102.2	85.0	75.2	138.0
Head circumference (cm) (SD)	46.2 (−2.9)	47.7 (−1.5)	45.6 (−1.9)	52.0 (−2.6)
Developmental milestones				
Walk alone (months)	15	12	18	?
Meaningful words (months)	18	23	18	?
Intelligence	IQ = 71	IQ = 88	DQ = 81	normal

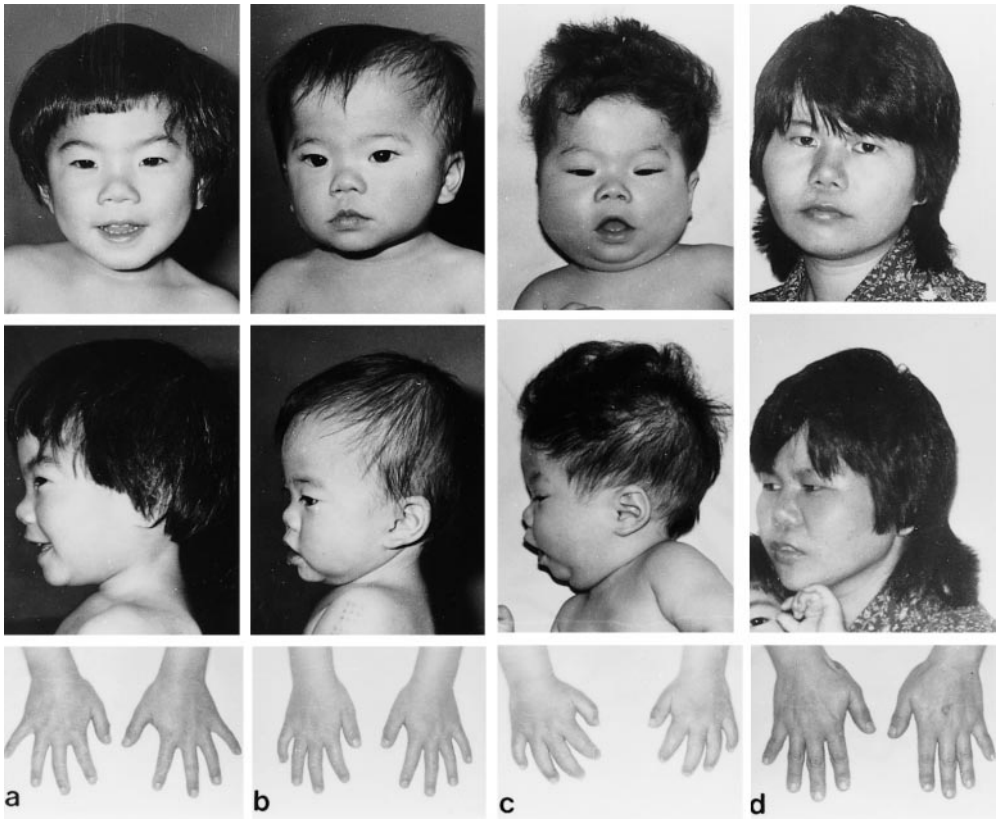

Fig. 1 **a** Patient 1 at 3 years 7 months. **b** Patient 2 at 1 year **c** Patient 3 at 7 months. **d** Their mother (Informed consent was obtained for the use of these photographs)

When seen by us at age 36 years, she weighed 47 kg (−0.8 SD), measured 146 cm (−2.1 SD) in height, had a head circumference of 52 cm (−2.6 SD), and her arm span was 138 cm. She had a narrow bifrontal diameter with a facial appearance similar to that of her sons. Synophrys, a short nose with anteverted nostrils and a short columella, and thin vermilion borders of the upper and lower lips were also present (Fig. 1d), as well as small hands with short fifth fingers. She had graduated from a 4-year college and had above-average intelligence.

The maternal grandparents (I-3 and I-4) and a maternal aunt (II-9) were all healthy and phenotypically normal. The father (II-7), aged 37 years, measured 159 cm (−1.9 SD) in height and had a head circumference of 55 cm (+0.03 SD), and his arm span was 161 cm. He was phenotypically and mentally normal.

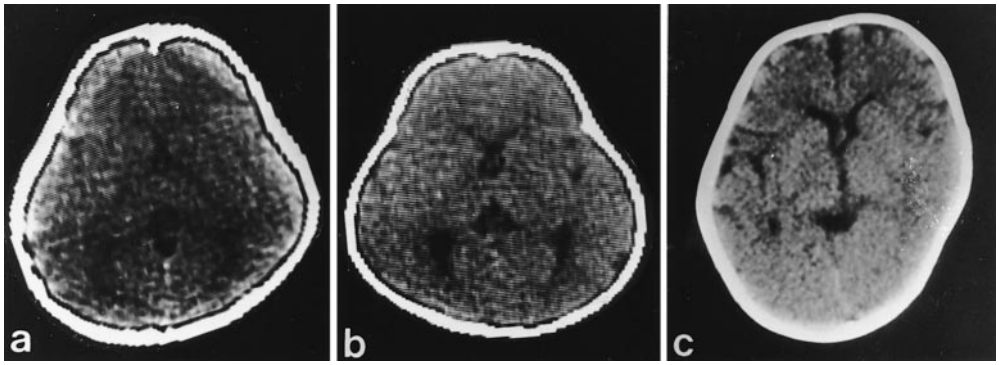

Fig. 2 Computed tomography scans of patients 1–3

Table 2 Clinical findings of patients 1–3 and their mother

Clinical findings	Patient 1	Patient 2	Patient 3	Mother
Microcephaly	+	−	+	+
Trigonocephaly	+	+	−	+
Short stature	−	+	+	+
Narrow bifrontal diameter	+	+	+	+
Upslanting palpebral fissures	+	+	+	+
Synophrys	+	+	+	+
Short nose	+	+	+	+
Anteverted nostrils	+	+	+	+
Short columella	+	+	+	−
Thin upper lip	+	+	+	+
Micrognathia	+	+	+	+
Short neck	+	+	+	+
Low hair line	−	−	+	−
Micromelia	−	+	+	+
Small hands	+	+	+	+
Short fifth finger	+	+	+	+
Inguinal hernia	+	+	+	−
Dermatoglyphics				
Distally placed axial triradii	+	+	+	−
Thenar loop patterns	+	−	−	−
Total finger ridge count	109	117	116	103
Karyotype	46,XY	46,XY	46,XY	46,XX

Other abnormalities: patient 1: abnormal EEG, hyperopia.

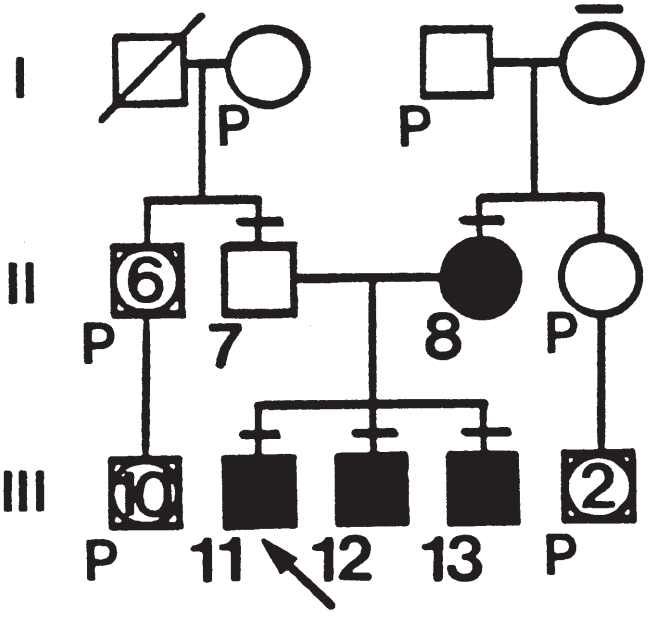

Fig. 3 Pedigree of the family. P: photographs examined.

X-ray examination

Abnormal radiographic findings included short fingers and toes with short middle phalanges in all three brothers and their mother, and mild digital markings of the skull in patient 1. In all the patients, the carpal bone age corresponded to the chronological age. Computed tomography scans in patients 1 and 2 showed a narrow bifrontal diameter (Fig. 2). Results of intravenous pyelography in patients 1 and 2 were normal.

Dermatoglyphics

Patient 1 had a distally placed palmar axial triradii. A loop-distal pattern was noted in the right thenar area. Total finger ridge count (TRC) was 109. Right fingers: ulnar loop (Lu), Lu, Lu, Lu, Lu; left fingers: Lu, Lu, Lu, whorl (W), W. Patient 2 had a distally placed palmar axial triradii. TRC was 117. Right fingers: Lu, Lu, Lu, W, Lu; left fingers: Lu, Lu, Lu, W, W. Patient 3 had a distally placed palmar axial triradii. TRC was 113. Right fingers: Lu, radial loop (Lr), W, W, W; left fingers: Lu, Lu, Lu, W, W. Mother: TRC was 193. Right fingers: Lu, Lu, W, W, Lu; left fingers: Lu, Lu, Lu, W, Lu.

Discussion

The three brothers described here shared several clinical manifestations (Tables 1 and 2). They included short stature with short span length, microcephaly, a peculiar facies with synophrys, cupid-bow shaped lips with a thin vermilion border of the upper lip, a short nose with anteverted nostrils, a short collumela, micrognathia, micromelia, and mild mental retardation.

The clinical features of the brothers and their mother are distinct. The combination of the clinical features described

in these three brothers has not been reported in the literature. The disease shares some clinical features with mild Brachmann–de Lange syndrome, whose clinical manifestations are extremely variable, including microcephaly, craniofacial appearance, small hands, and borderline intelligence or mild mental retardation (Ireland et al. 1993, Van Allen et al. 1993). Postnatal growth retardation in our patients was mild. The eyebrows were not characteristically "pencilled". They lacked a crescent-shaped mouth. Thus, the facial features were different from those of Brachmann–de Lange syndrome. In addition, they lacked any feeding dysfunction during the neonatal period, neurological impairment or behavioral problems, which are also characteristics of Brachmann–de Lange syndrome. Altogether, the facial appearance and the overall pattern of clinical manifestations in our patients are similar but distinct from those of Brachmann–de Lange syndrome. The disease also shares several clinical features with Opitz trigonocephaly syndrome (C syndrome)(Opitz et al. 1969). These features include microcephaly, a narrow forehead with trigonocephaly, upslanting palpebral fissures, micrognathia, and cryptorchidism. However, the patients lacked clinical features characteristic of Opitz trigonocephaly syndrome, including facial phenotype, polydactyly, a midline palatal furrow, multiple frenula, cardiac anomalies, and flexion deformity of the limbs. In addition, Opitz trigonocephaly syndrome is an autosomal recessive disorder. Thus, we can conclude that the disease is different from Opitz trigonocephaly syndrome. Kawashima and Tsuji (1987) reported a 26-year-old mother and her 21-month-old son with microcephaly, deafness, malformed ears, mild mental retardation, and a peculiar face. However, our patients lacked deafness and malformed ears, and their facial appearance was different from that of the above patients.

The syndrome was inherited vertically in this family with both sexes affected, and the clinical manifestations varied between the affected brothers and their mother. Thus, it seems that the condition in this family was transmitted as an autosomal or X-linked dominant trait with variable expressivity.

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