

3-M syndrome in two sisters

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Abstract: 3-M syndrome is a rare, autosomal recessive dwarfing syndrome characterized by prenatal growth restriction, facial dysmorphism and absence of both microcephaly and mental retardation. The term 3-M syndrome originates from the common initial of the first three authors of the first report. The diagnosis is established by a combination of clinical history, clinical examination and radiographic findings. The present report shows two sisters whose facial features were slightly different from those usually reported. In addition, they presented with small nails and abnormal dermatoglyphics. The present report expands the phenotypic spectrum of 3-M syndrome.

Key words: prenatal growth restriction; slender-bone dysplasia; 3-M syndrome.

The diagnosis of 3-M syndrome in a dwarfed child is based on a distinctive pattern of clinical history, clinical examination and radiographic findings.^{1–11} Any of the clinical signs taken separately has little specificity. The radiographic examination is abnormal but not diagnostic, as similar X-ray changes have been documented in other disorders.

CASE REPORT

Patient 1

This girl was the first child of young, unrelated parents. She was born by Caesarean section at 39 weeks, because of breech presentation. Her birthweight was 2000 g (–3.06 SD), length 38 cm (–5.27 SD). Because of low birthweight and mild respiratory distress, she was hospitalized for 2 months. Her discharge weight was 2680 g. Evaluation at 4 months showed facial dysmorphism characterized by dolichocephaly, frontal bossing, a flat nasal bridge, low-set ears and a high palate. Karyotype was 46XX (in one mitosis, deletion of the long arm of the X chromosome resulting in two fragments was noted). The diagnosis of 3-M syndrome was considered. At the age of 6 years, progressive scoliosis was noted and the patient underwent spinal bracing at the age of 7 years. Normal values for plasma growth hormone were obtained. She was referred to the Ambulant Centre for Defects of Locomotor Apparatus in Prague at the age of 14 years 5 months. Physical examination showed an intelligent, short girl with a weight of 35 kg (below 3rd centile), height of 125.6 cm (–6.1 SD). There was severe

shortening of the trunk and shortening of the extremities to a lesser degree (upper segment –7.0 SD, upper extremities –4.1 SD, lower extremities –3.7 SD).

The thorax was narrow in transverse diameter: thoracic index 77.6 (+1.4 SD). Head circumference was 55.5 cm (69 centile). Predicted adult height was 135 cm. She had a dolichocephalic skull, prominent forehead and low-set large ears. Her face was triangular with prominent cheeks, flattened malar regions, a short nose, flat nasal bridge, anteverted nares, epicanthal folds, a wide mouth, narrow lips with down-turned corners and a high palate. Her hair was coarse and her eyebrows prominent. Her shoulders were square in appearance. There was pectus excavatum with a scoliotic curve to the right (Fig. 1a). The mobility of the joints was normal, except for increased external rotation of the hips. There was mild genu valgum and pes planovalgus. There was clinodactyly of the 4th and 5th fingers, and the fingernails and toenails were small (Fig. 1b). The dermatoglyphics were abnormal. The finger's papillar pattern was that of simple arches and loops. There were hypoplastic flexion creases in the 3rd left finger and absence of distal interphalangeal flexion creases in the 4th and 5th fingers of both hands. The atd angles and the palmar flexion creases were normal. The atd angle is one of the main topographical points or areas of the palm and is localized near the proximal margin of the palm between the thenar and hypothenar eminences. It is formed where three papillary ridges of the hand come together (triradius). The left wrist crease consisted of two distinct creases. There were normal secondary sexual characteristics (Fig. 1a). Laboratory examinations showed normal white blood cell, red blood cell and platelet counts, and normal serum calcium, phosphorus, isoenzymes of bony

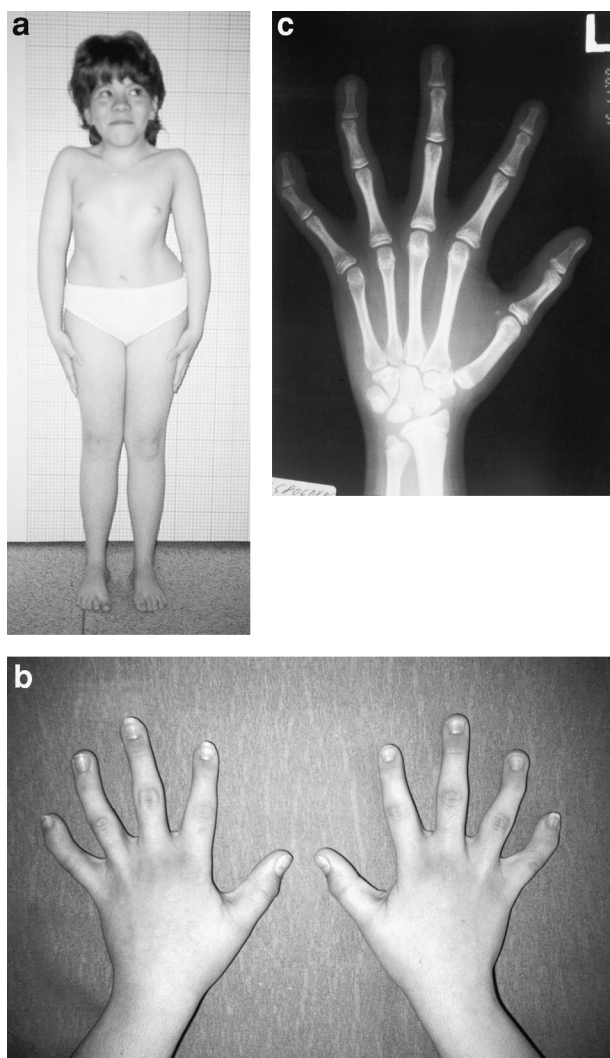


Fig. 1 12-year-old girl with 3-M syndrome. Note: (a) prominent cheeks, epicanthal folds, large ears, wide mouth, and narrow lips; (b) small hands, clinodactyly of the fourth and fifth fingers, and small nails; (c) slender tubular bones, subluxation in the distal interphalangeal joints, distal shortening of ulna; bone age corresponds to the chronological age.

alkaline phosphatase and osteocalcin levels. Collagen cross-links in the urine were mildly elevated. The urinary oligosaccharides and amino acid values were normal.

Radiograms documented right-sided thoracolumbar scoliosis, slender tubular bones and ribs, narrowed cortex of the long bones, shortened distal ulna, subluxation in the distal interphalangeal joint of the 5th finger, short femoral necks, foreshortened lumbar vertebral bodies, spina bifida L5 and S1 and

lateral position of the patellae. The bone age of the hands was consistent with the chronological age (Fig. 1c).

Patient 2

The younger sister of patient 1 was born after a term, uneventful pregnancy. Her birthweight was 1900 g (-5.27 SD), length 38 cm (-5.27 SD). She was referred to the Ambulant Centre for Defects of Locomotor Apparatus at the age of 10 years (Fig. 2). Physical examination showed an intelligent, short girl with a weight of 17.0 kg (75 centile) and height of 102.8 cm (-5.8 SD). Shortening of the extremities was more severe than that of the trunk (upper segment -4.7 SD, lower segment -5.1 SD, upper extremities -4.1 SD). Thoracic index was 55.8 (-1.7 SD) and she had a head circumference (occipitofrontal circumference) of 53.0 cm (65 centile). Predicted adult height was below 135 cm. Her facial dysmorphic features were similar to those of her older sister (Fig. 2). The dermatoglyphics were abnormal. The fingers' papillar pattern was that of simple arches and loops. The distal flexion creases of the right 2nd–4th fingers were hypoplastic. The atd angles were elevated: left 53 degrees, right 49 degrees. There was a simian crease on the left. The number of secondary flexion creases was increased bilaterally. The wrist creases were normal. The only difference between this patient and her sister in the biochemical investigations was normal values of the collagen cross-links in her urine. The only radiographic differences were an absence of kyphoscoliosis and dislocation of the distal interphalangeal joint of the little finger, and normal length of ulna.

DISCUSSION

Since the first descriptions by Miller *et al.* in 1975 and Spranger *et al.* in 1976, approximately 20 cases of 3-M syndrome have been reported.^{1–4,7–11} The distinctive features of this rare and little known syndrome are prenatal growth restriction, facial dysmorphism (triangular face, pointed chin, prominent mouth and lips, fleshy nose with anteverted nares) and an absence of both microcephaly and mental retardation. It is probable that 3-M syndrome is often misdiagnosed or not recognized because of normal mental development, slight dysmorphic facial features and good health of the patients. The set of clinical and radiographic changes in the sisters in the present report is consistent with 3-M syndrome in spite of some atypical features.

These atypical features include large low-set ears, epicanthal folds, wide mouth with down-turned corners, narrow lips, high palate and small nails. Abnormal dermatoglyphics were also documented by Miller *et al.* and Spranger.^{7,9} Kyphoscoliosis is rare but has been reported in other cases.³ The remaining clinical features (short stature, triangular face, large cranium, prominent forehead) and the clinical history (low birthweight in full term infant) are typical of 3-M syndrome. The parental facial appearance was normal. Clinodactyly of the 5th fingers was present in the mother. Family medical history was unremarkable. Radiographic examination in the patients showed all the features reported in 3-M syndrome, such as slender tubular bones and ribs, foreshortened lumbar vertebral bodies, high vertebral bodies, spina bifida occulta and short

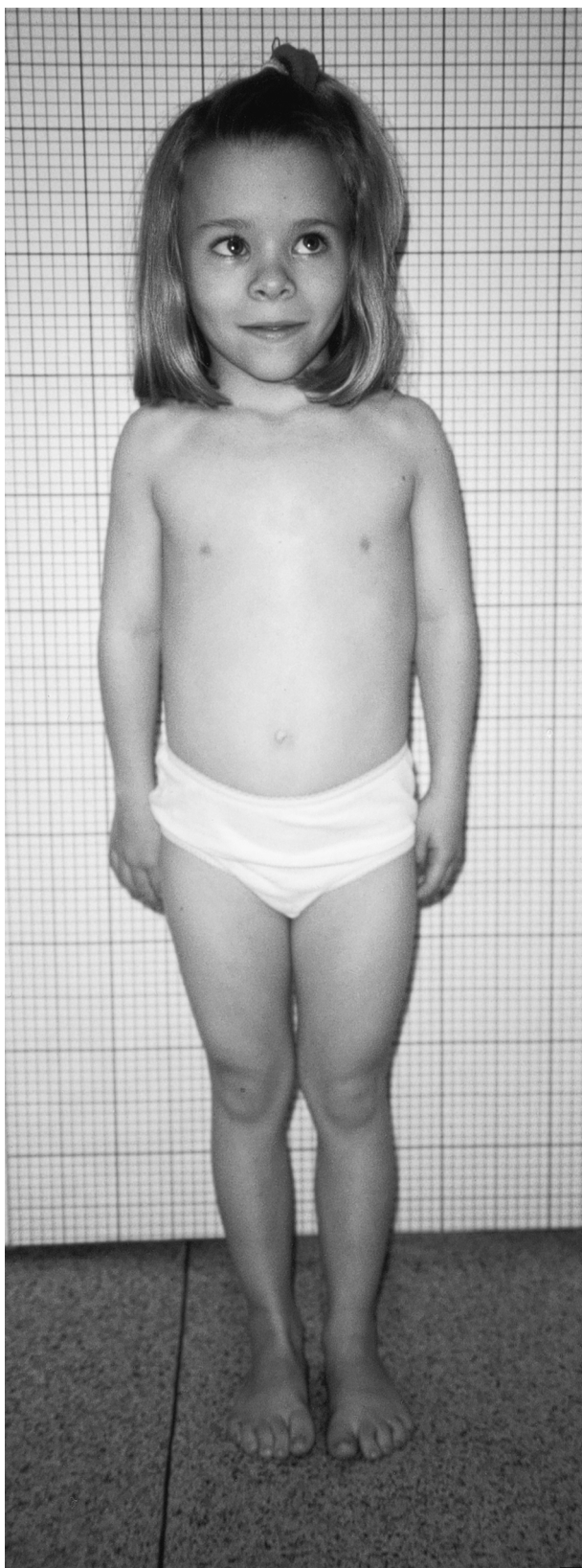


Fig. 2 10-year-old girl with 3-M syndrome. Note similarity to her sister (Fig. 1a).

femoral necks. The more severely affected older sister had distal shortening of ulna and kyphoscoliosis.

The differential diagnosis of our patients is Silver–Russell syndrome.^{9,10} Silver–Russell syndrome is characterized by a pseudohydrocephalic appearance. Frequently associated features, such as asymmetry, abnormal pattern of sexual development, mental retardation and chromosomal abnormalities, were all absent in the present cases. Other short stature–slender bones syndromes, such as fetal alcohol syndrome, Seckel bird-headed dwarfism, Bloom's syndrome and mulibrey nanism are unlikely to cause confusion, as microcephaly and mental retardation, major clinical signs of these syndromes, were absent in the present cases and neither sister showed eye, skin or cardiac abnormalities.^{9,10} Moderate intrauterine growth retardation, postnatal dwarfism, normal mental development and slender bones are major features of gloomy face syndrome. However, the facial dysmorphism of this syndrome (a gloomy round face with a short bulbous nose) is quite different from that of 3-M syndrome.⁶

3-M syndrome is inherited as a recessive trait. The aetiology of the condition is uncertain. Joint hypermobility and dislocations have been noted in some patients and a report of a fatal case with cerebral aneurysm suggests that 3-M syndrome could be a generalized disorder of connective tissue. Measurable low-collagen type III in skin fibroblasts of one case supports this possibility.⁴ The importance of the skeletal survey is that it excludes with certainty other causes of short stature, such as bone dysplasias and mucopolysaccharidoses.

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