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Markers for Bone Metabolism in a Long-Lived Case of Thanatophoric Dysplasia

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Abstract. We report a male patient with type 1 thanatophoric dysplasia, now eight years old, having a mutation in the FGFR3 gene. Radiological examination at birth revealed that the ribs and the bones of the extremities were very short and vertebral bodies were greatly reduced in height with wide intervertebral spaces. The femurs were shaped like French telephone receivers. Because of respiratory insufficiency due to the narrow thorax, the patient has been intubated and supported by continuous mechanical ventilation since the day after birth. Since 5 years of age, despite sufficient caloric intake, his body weight never increased above 4700 g, body height 49.0 cm, head circumference 46.1 cm, and chest circumference 35.8 cm. Acanthosis nigricance and huge bilateral coral-like urolithiases has been present. His mental development was severely retarded but he was able to make emotional expressions. Although developments in motor functions could not be assessed, his neurodevelopmental milestones in social relationships and langage perception seemed to be at the level of a 10 to 12 month old. His bone maturation was also severely retarded. All of the assays of his serum and urinary bone formation- or resorption-related substances were within normal limits for age. Therefore, bone formation as well as bone resorption activities seemed normal and not responsible for his growth retardation.

Key words: Fibroblast growth factor receptor 3, Growth, Development, Acanthosis nigricance

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THANATOPHORIC dysplasia is an extreme skeletal dysplasia with micromelia, relative macrocephaly, platyspondyly and reduced thoracic cavity. We report a male patient with thanatophoric dysplasia, now eight years old, whose growth is severely retarded. A missense mutation in the fibroblast growth factor receptor 3 (FGFR3) gene was found in this patient and reported elsewhere by Katsumata *et al.* [1]

Case report

By fetal ultrasonographic examination at 28 weeks of gestation, the male patient, now eight years, was revealed to have short limbs and hydramnios. He was delivered after 48 weeks of gestation by Caesarean section. Apgar scores were 7 points at one min and 9 at five min. His birth weight was 2600 g, length 37.0 cm, head circumference 37.0 cm and chest circumference 26.8 cm. His short length, relatively large head, narrow thorax and short extremities were noted. Radiological examination (Fig. 1a) revealed that the ribs and the bones of the extremities were very short and vertebral bodies were greatly reduced in height with wide intervertebral spaces. The femurs were shaped like French telephone receivers. The mother was 20 years old, and the father 25 years when the patient was born. The parents were healthy and unrelated. There was no family history of skeletal deformity and the two younger siblings of the patient, a sister and a brother, were healthy.

Because of respiratory insufficiency due to the narrow thorax, the patient has been intubated and supported by continuous mechanical ventilation

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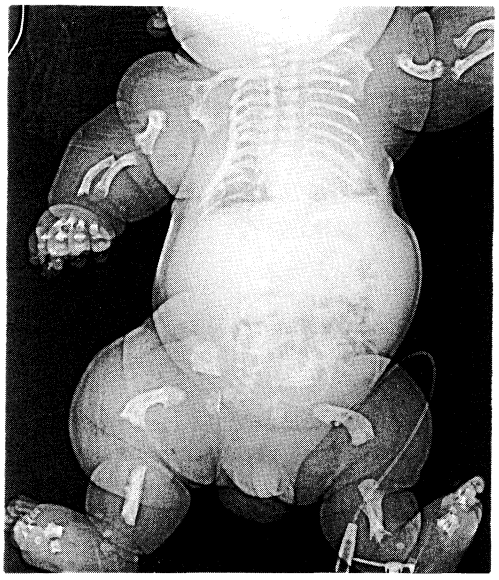

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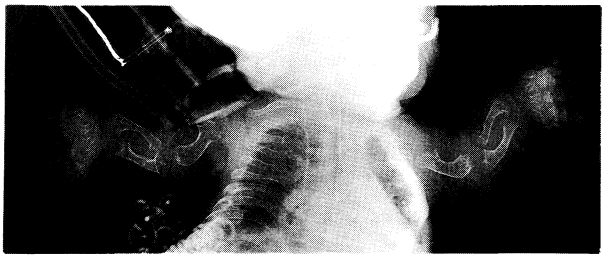

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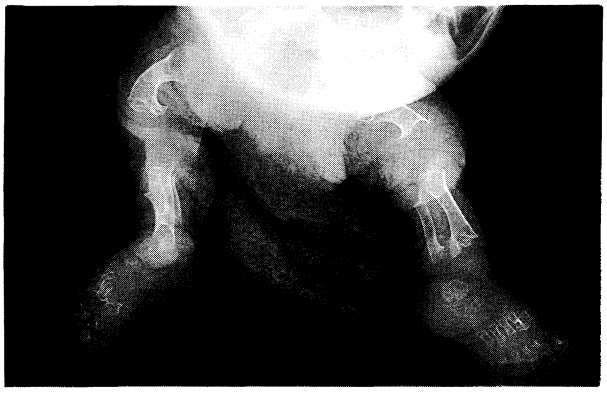

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Fig. 1. Bone X-ray at 2 months of age (Fig. 1a) and 7 years of age (Fig. 1b and 1c). At both ages, the ribs and bones of the extremities were very short and the vertebral bodies were greatly reduced in height with wide intervertebral spaces. The femurs were shaped like French telephone receivers. Epiphysial maturations at 7 years were greatly retarded and essentially at the same level as at 2 months of age.

since the day after birth. Tracheotomy was not performed in accordance with his parents' decision. Trivial infections have been frequent but not life threatening.

Since 5 years of age, despite sufficient caloric intake, 500 kcal (2.1 MJ)/day, his body weight never increased above 4700 g, body height 49.0 cm, head circumference 46.1 cm, and chest circumference 35.8 cm (Fig. 2). He had been fed a liquid mixture augmented with trace elements. No cloverleaf skull anomaly was observed and his anterior fontanell was already closed. Acanthosis nigricance has been present since 2 years of age (Fig. 3). His mental development was severely retarded but he was able to make emotional expressions. Although developments in motor functions could not be assessed, his neurodevelopmental milestones in social relationships and langage perception seemed to be at the level of a 10 to 12 month old. At eight years, his total

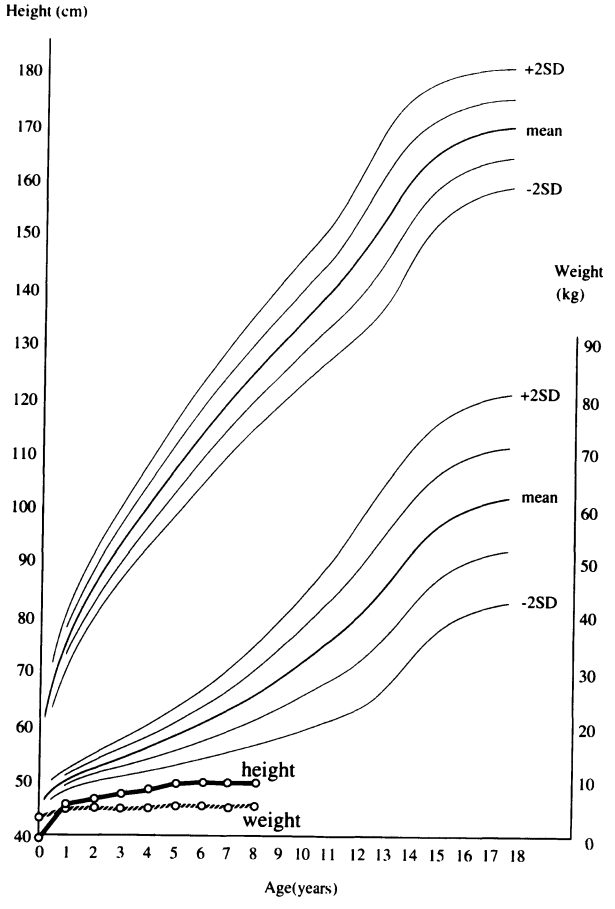

Fig. 2. Growth curve of the patient. The solid line is for height and the broken line for weight.

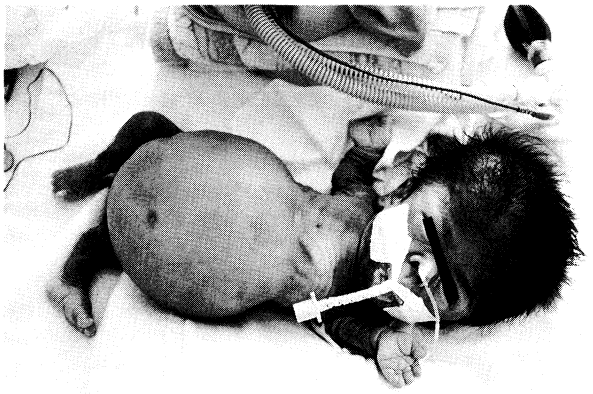

Fig. 3. A photograph of the patient at 7 years of age. Note generalized hyperpigmentation due to acanthosis nigricance and the absence of cloverleaf skull anomaly.

serum alkaline phosphatase was 449 IU/L (normal 350 to 900 IU/L at 8 years), total acid phosphatase 12.6 IU/L (normal 8.5 to 22.5 IU/L at 8 years), calcium 4.7 mEq/L and inorganic phosphate 4.3 mg/dL. His total IGF-1 was as low as 26 ng/mL, IGF-BP III as low as 0.60 μg/mL (normal 1.78 to 4.43 μg/mL at 8 years), mid-molecular PTH 386 pg /mL (normal adult 145 to 500 pg/mL), osteocalcin 5.6 ng/mL (normal adult 1.5 to 6.5 ng/mL), pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) 4.4 ng/mL (normal 4.1 to 16.8 ng/mL at 10 years [2]), and carboxyterminal propeptide of type I procollagen (PICP) 293 ng/mL (normal 147 to 546 ng/mL at 10 years [2]). The calcium creatinine ratio in the urine was as high as 0.5 to 1.2. Urinary excretion of deoxypyridinoline was 19.1 μmol/mol creatinine (normal adult 2.1 to 5.4, normal children four- to five-fold higher than in adults), and N-telopeptide of type I collagen (NTx) 252 nmol bone collagen equivalents/mmol creatinine (normal adult 13 to 73, normal children four- to five-fold higher than in adults). Thyroid and renal functions were normal. Between 3 and 6 years, he has had occasional hypoglycemia with ketonuria and suppressed insulin secretion, thought to be due to ketotic hypoglycemia. The status of epiphysial maturation at 7 years was markedly retarded and essentially the same as at 2 months of age (Fig. 1b and 1c). In addition, at age 6 an ultrasound examination revealed huge bilateral coral-like urolithiases, which did not impair his renal functions. Head CT visualized mild brain atrophy.

Discussions

Thanatophoric dysplasia, caused by mutations in the FGFR3 gene, is divided into two subtypes based on the presence of curved as opposed to straight femurs. Our patient, a type 1 with curved, short femurs, had a missense mutation in the FGFR3 gene [1].

All of the assays of serum and urinary bone formation- or resorption-related substances were within normal limits for age. Therefore, bone formation as well as bone resorption activities, both of which are essential for growth [3, 4], seemed normal and not responsible for his growth retardation. Hypercalciuria and urolithiasis were possibly the results of immobilization itself and therefore independent of the patient's bone pathophysiology. Growth hormone deficiency was suggested by low concentrations of serum IGF-BP III as well as IGF-1. But it was unlikely that growth hormone deficiency by itself caused severe growth retardation in this systemic bone disease.

The cause of acanthosis nigricance, reported in other long-lived patients [5, 6], is not known.

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