CASE REPORT

Thanatophoric dysplasia Variant in Identical Saudi Twins; Prenatal Diagnosis and Genetic Analysis

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Abstract

Thanatophoric dysplasia is the most common neonatal lethal skeletal dysplasia with an estimated incidence of 1 in 20,000 live births. This condition shares some similarity of radiological findings with other types of lethal skeletal dysplasias. Definite diagnosis is necessary for accurate medical and genetic counseling. Prenatal sonographic and molecular genetic diagnoses in identical twin pregnancy of variant phenotypic appearance TD type I, is presented here.

Keywords: Thanatophoric dysplasia (TD), dwarfism, Fibroblast Growth Factor Receptor 3 (FGFR3)

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Introduction

Congenital disorders of the bones are a heterogeneous group of disorders that include skeletal dysplasias, bone metabolic disorders, dysostoses, and skeletal malformation and/or reduction syndromes. (1)

Thanatophoric dysplasia is a lethal skeletal dysplasia divided into two subtypes. Type I is characterized by extreme rhizomelia, bowed long bones, narrow thorax, a relatively large head, normal trunk length and absent cloverleaf skull. The spine shows platyspondyly, the cranium has a short base, and, frequently, the foramen magnum is decreased in size. The forehead is prominent, and hypertelorism and a saddle nose may be present. Hands and feet are normal, but fingers are short. Type II is characterized by short, straight long bones and cloverleaf skull. (2) Because of this diversity, the diagnosis is usually based on a combination of clinical, ultrasonographic, radiological, and molecular studies during pregnancy. Despite recent and considerable improvements in imaging tools and in molecular biology, prenatal diagnosis of congenital bone disorders remains a clinical challenge. Twin pregnancy in particular MC twins, have an increased risk of congenital anomalies than singleton. Among twin

pregnancies, the rate of congenital anomalies in MC twin pairs was nearly twice that in DC pairs.[3] That is, affecting only one of the siblings in both dizygotic (DZ) and monozygotic (MZ) twins. They can occur in both dichorionic and monochorionic twins. Discordant abnormalities caused by genetic disorders have been described mainly in DZ twins, but rarely in one of a MZ twin pair.[4, 5] We reviewed a different type of severity of variable degree of TD in a set of complicated twin-pregnancy, which imposed the difficulties we encountered in the diagnosis and early counseling.

Case Report

A Saudi female is 21 years old, G2 P1 and her husband is 36 years old. Both had normal stature and there was no consanguinity. In the second trimester, ultrasound showed, a twin pregnancy with severe limb shortening, a small thorax, and polyhydramnios were detected in one fetus, with milder skeletal abnormalities in the other one. After caesarean section at 37 weeks gestational age, twin 1 were baby girl had marked limb shortening, a small thorax, brachydactyly, macrocephaly without a clover-leaf skull, and a flat nasal bridge. Length was 38 cm (< 10th centile), weight 2080 g (>25th centile and < 50 centile) and occipitofrontal circumference 36 cm (>50th centile).(Figure 1-A) Radiographic findings were compatible with a diagnosis of TD type 1 (Figure 1-B,C), including short horizontal ribs and a small thorax, short long bones with bowing and "French telephone receiver" appearance of the femora, small iliac bones, horizontal acetabular roofs, small sacroiliac notches, marked flattening of the vertebral bodies, a large calvarium with short, narrow skull base, absent cloverleaf skull, and extreme shortening and broad appearance of the tubular bones of the hands and feet. The infant died on the third day of life from respiratory failure. Twin 2 has milder and form of TD (Figure 2-A). Birth weight is 2.038kg, (>25th centile and < 50 centile) length 40 cm (< 10th centile), and head circumference 37cm (>50th centile). The baby has relatively short long bones, small thorax, flattening of the vertebral bodies, a large calvarium with short, and absent cloverleaf skull.(Figure 2-B) she required minimal oxygen support and stayed in the nursery for six months without invasive measurements. She expired because of respiratory infection and the family agreed not to resuscitate her. Molecular analysis of Fibroblast Growth Factor Receptor 3 (FGFR3) gene identified, (R248C).T

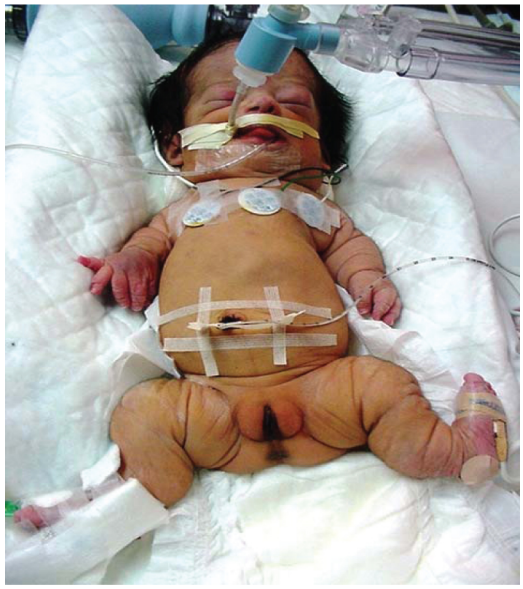

Figure 1- A: *Twin 1 (Severe Form TD)*

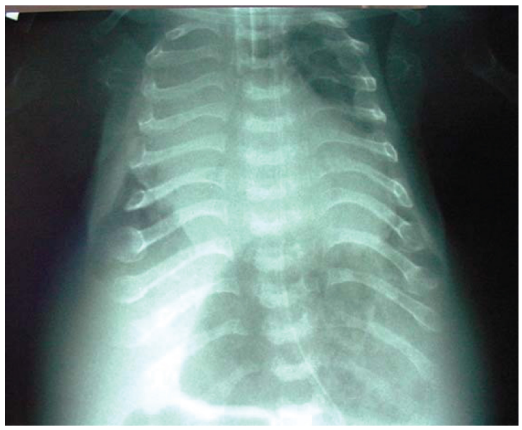

Figure 1- B: *(Twin 1) Radiographic findings were compatible with a diagnosis of TD type 1 short horizontal ribs and a small thorax and marked flattening of the vertebral bodies*

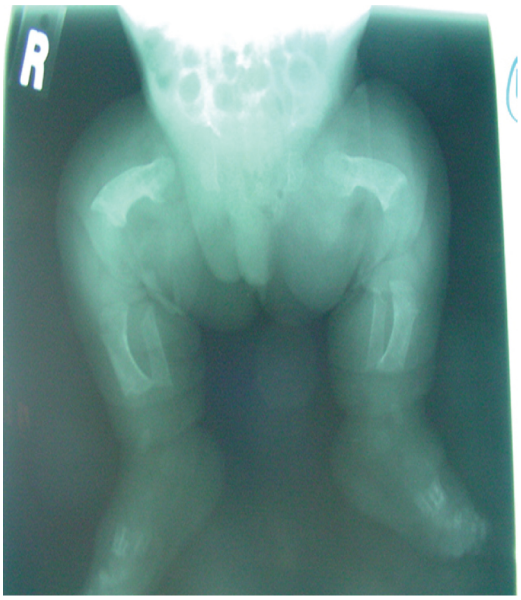

Figure 1 – C: *(Twin 1) X ray lower extremities. Bowing and French telephone receiver appearance of the femora, small iliac bones, horizontal acetabular roofs, small sacroiliac notches.*

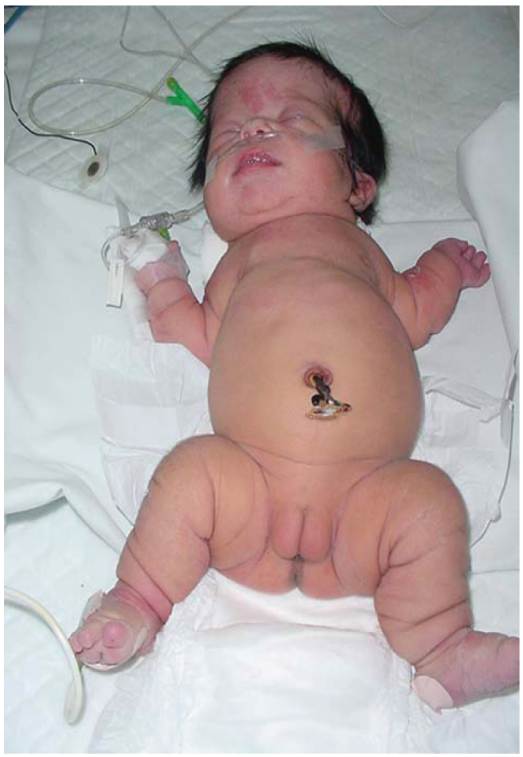

Figure 2-A: *Twin 2 (Mild Form)*

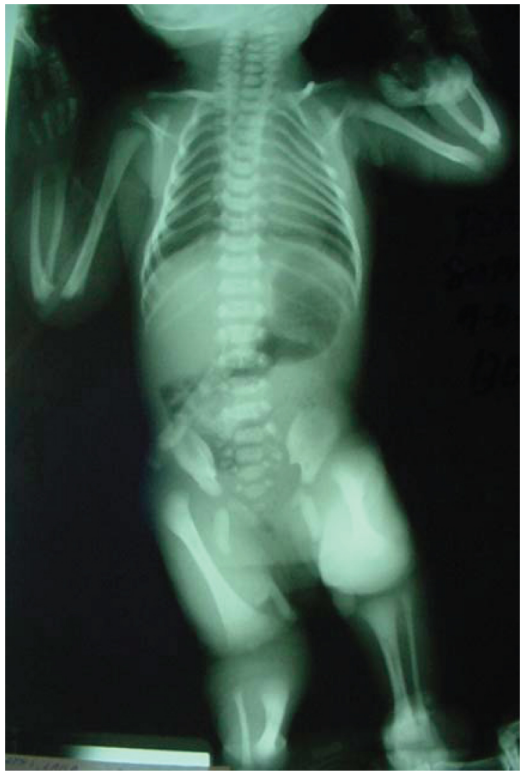

Figure 2- B: Twin 2 baby-gram (Mild form of TD) Relatively short long bones, mild small thorax, flattening of the vertebral bodies.

Discussion

Most cases of TD are sporadic. [6] Autosomal dominant inheritance is supported by the presence of affected monozygotic twins. [7,8]

Absence of parental consanguinity lead to the possibility of paternal age effect, and high new mutation rate. The finding of TD in this twin with out cloverleaf skull who was the products of normal, non-consanguineous parents'1 probably reflects germline mosaicism rather than autosomal recessive inheritance. Overall, it has been estimated that both twins are affected for the same anomaly in approximately 15% of cases. [9] Thanatophoric dysplasia can be caused by as many as 12 distinct missense fgfr3 mutations. Of these, the missense mutation 724 C Y T, causing an arginine to cyseine substitution (R248C), is the most often. [10] At least 102 cases of R248

mutation associated with TD1 have been reported.[11] This kind of different phenotypic features in the same set of twin pregnancies is the first case to be reported according to our Pubmed research. Molecular analyses of the fgfr3 gene in the present study revealed a R248C mutation in the twin infant which raises the possibility to be the frequent mutation in our population which needs more data collection to reach to such conclusion. Since R248C is the most common mutation in TD type 1, molecular analysis of the fgfr3 gene for this mutation is useful for early and rapid screening of fetuses with ultrasound findings suggestive of TD and therapeutic abortion can be an option for the parents.

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