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Thanatophoric Dysplasia Type 1 (TD1) without "Telephone Receivers"

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Abstract Thanatophoric dysplasia (TD) is a relatively common neonatal lethal skeletal dysplasia. It is subdivided into type 1 (TD1) and type 2 (TD2). By definition, TD1 is differentiated from TD2 by bowed femori, the so called "telephone receivers". TD2 is distinguished by straight femori and cloverleaf skull deformity. We described a case of TD1 with atypical feature of almost straight femori, and was found to have characteristic TD1 missense mutation C746G in *FGFR3* gene.

Key words Bowed femori; *FGFR3* gene; TD1; Thanatophoric dysplasia

Introduction

Thanatophoric dysplasia (TD) is a common neonatal lethal skeletal dysplasia. It is classified into type 1 or 2 on the shape of femori, presence of cloverleaf skull deformity and specific *FGFR3* mutations. Other variants of TD, San Diego type and the Torrance-Luton type have been described. Features common to all include macrocephaly, short ribs, and narrow thorax. Cause of death is respiratory insufficiency that occurs shortly after birth. Respiratory insufficiency may be secondary to a small chest cavity and lung hypoplasia, compression of brain stem by narrow foramen magnum, or a combination of both.[1] Diagnosis is usually suspected by antenatal ultrasound examination and confirmed by molecular analysis on amniocytes.

Thanatophoric dysplasia occurs in approximately 1/20,000 to 1/50,000 births.[2] *FGFR3* is the only gene known to cause TD.[3] It was mapped to chromosome 4p16.3, and consisted of 19 exons that spanned over 16.5 kb. There is 100% penetrance of *FGFR3* mutations and no phenotype-genotype correlation for reported mutations.

Thanatophoric dysplasia type I is caused by de novo autosomal dominant mutations in the *FGFR3* gene. Recurrence risk is low. Germline mosaicism in healthy parents remains a theoretical possibility. Prenatal diagnosis is clinically available.

We report a case of full term TD1 with almost straight femori but had a common TD1 mutation in the *FGFR3* gene.

Subject, Methods and Results

Proband was a male, born at gestation of 36+4 weeks to non-consanguineous parents of Chinese ethnicity. At time of conception, father was aged 48 and mother was 25. He was a Para 1 baby delivered by Lower Segment Caesarean

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Section because of antenatally suspected skeletal dysplasia. Initial antenatal follow up was in china, and there was a history of threatened miscarriage at 8 weeks gestation. Ultrasound examination at 34 weeks gestation in Hong Kong showed severe micromelia (femur length corresponded to 18 weeks and humerus to 16 weeks gestation), macrocephaly (38 weeks size) and small chest (27 weeks size). His birth weight was 2.68 kg with apgar Scores of 6 at both 1 and 5 minutes. He was noticed to have poor respiratory effort with gasping at birth; and required active resuscitation, together with assisted ventilation via tracheal intubation. There was no family history of short stature, fetal death or skeletal dysplasia.

On examination, proband was dysmorphic (Figure 1) with macrocephaly (head circumference 38 cm, >97th centile) and large anterior fontanelle (> 4 cm across), frontal bossing, flat nasal bridge, short limbs (rhizomelic), trident hands and short fingers. The thoracic cage was small with poor expansion and decreased breath sound. He had a protuberant abdomen and hepatomegaly (4 cm below the costal margin). Cardiovascular examination was normal. Ultrasonogram of brain showed dilated lateral and third ventricles. Blood for molecular analysis for thanotophoric dysplasia was sent to Clinical Genetic Service on day 1.

Immediate postnatal babygram (Figure 2) showed macrocephaly with small facial bones, relative long trunk with short limbs, short ribs, narrow thorax, atypically shaped femori with no resemblance to the shape of "telephone receivers", and generalised flattening of vertebral bodies. Characteristic ovoid lucent appearance of femori in TD1 is present on the right side and bilateral proximal humeri. Hypoplastic ilia were seen with narrowed sacral-sciatic notch. Pubic and ischial bones were short and broad.

Postnatal course was complicated by multiple problems. Transient hypotension developed on day 1 was stabilised by two boluses of normal saline. No inotropes was required. Subsequent respiratory distress necessitated intermittent positive pressure ventilation with tracheal intubation. Chest expansion remained poor possibly due to underlying lung hypoplasia and did not respond well to assisted ventilation. There was recurrent respiratory acidosis. Proband was kept nil by mouth. Renal function and output had been normal during the stay. Transient hypocalcaemia was corrected by intravenous supplement. Routine septic work up was performed on day 1 and he was covered empirically with standard penicillin G and cefotaxime before definitive diagnosis was reached. Blood culture result expectedly came back negative and C-reactive protein level was normal. Antibiotics were taken off on day 3.

Parents had been informed of the possible diagnoses right from the start, and were involved in the care with our multi-

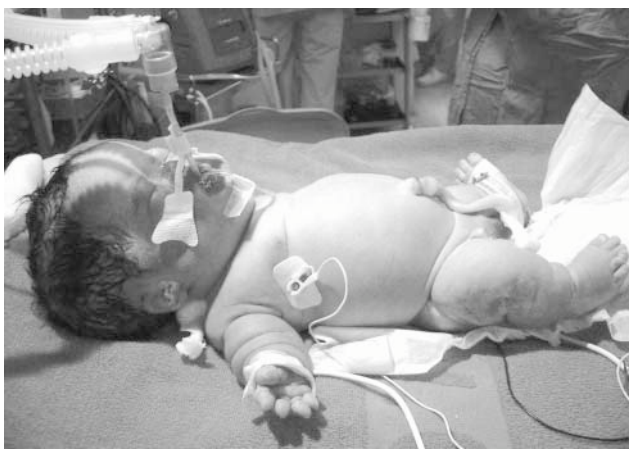

Figure 1 Proband with macrocephaly, narrow thorax, protuberant abdomen, trident hands.

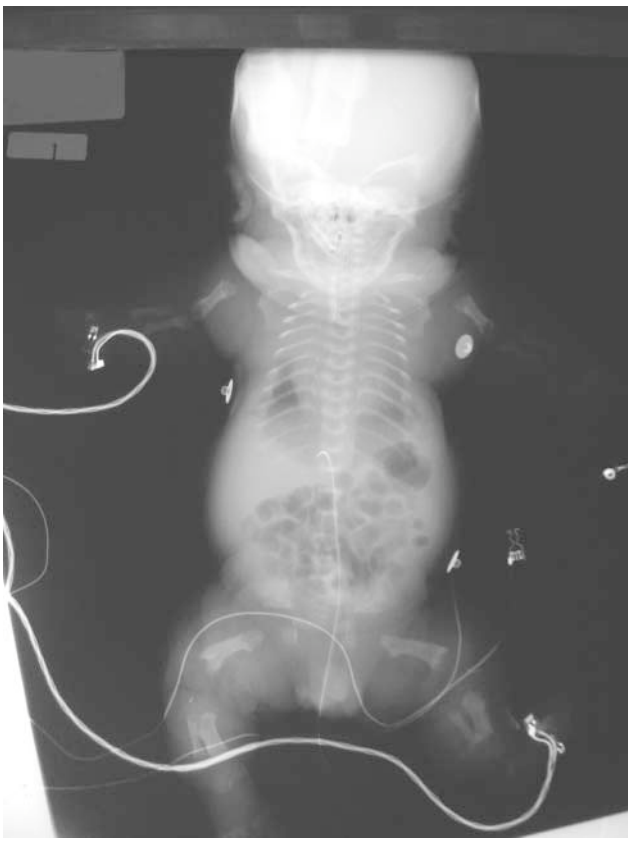

Figure 2 Babygram of proband with atypically shaped femori.

disciplinary team throughout this extremely stressful perinatal period; and gradually accepted the poor prognosis of the baby. Adequate counselling and support by the medical team was given to parents when the diagnosis of TD1 was confirmed on mutational analysis. Withdrawal of ventilatory support after full consultation and counseling with parents, was finally carried out on day 8. Mutational analysis confirmed a heterozygous c.746C>G mutation in the *FGFR3* gene and the diagnosis of thanatophoric dysplasia type 1. Parents were referred for genetic counselling.

FGFR3 fragment containing nt746 was amplified by polymerase chain reaction (PCR) for direct sequencing. The forward and the reverse primer were described by Tavormina et al.[4] After initial 4 min denaturing at 95°C, PCR was cycled 10 times at 95°C for 30 sec, at 50°C for 30 sec, at 72°C for 2.5 min and 20 times at 95°C for 30 sec, at 50°C for 30 sec, at 72°C for 2.5 min with auto-extend by 5 sec per cycle in a 50 µl mixture containing 1 x GC-rich PCR reaction buffer, 0.1 mM each dNTP, 0.2 mM each primer, 15 µl of 5M GC-rich resolution solution and 2 units enzyme mix (Roche, Germany). PCR products were purified using the QIAquick PCR purification kit (Qiagen, Germany) and sequenced on both strands with BigDye terminator chemistry by the standard protocols (Applied Biosystems).[4]

Parental DNA was analysed by direct sequencing for the specific mutation identified in the proband.

A heterozygous c.746C>G transversion mutation was found in the *FGFR3* gene. This is a de novo missense mutation that resulted in a change in amino acid code from Serine to Cysteine at codon 249. This mutation is not found in either parent.

Parents were counseled the nature of thanotophoric dysplasia, likely sporadic and the recurrence risk is very low. Prenatal diagnostic testing by either chorionic villous sampling or by amniocentesis is available for future pregnancy.

Parental consent for publication that included photos and radiographs was kindly given and signed.

Discussion

Thanatophoric dysplasia type 1 (TD1) and 2 (TD2) have similar clinical and radiological features. Femori in TD1 are bowed whereas in TD2, they are straight.[3] Cloverleaf skull if present is more suggestive of TD2 than TD1. It is interesting to note that the proband did not have the typical "telephone receiver" shaped femori while all other features were compatible with TD1.

FGFR3 is the only gene known to cause TD1 and TD2. Specific mutation K650E has been identified in all cases of TD2. Reported mutations of TD1 responsible for at least more than 90% of cases include missense mutations (80%) (R248C, Y373C, S249C, G370C, S371C), and nonsense mutations (10%) (X807L, X807G, X807R, X807C, X807W). The mutation found in the proband was a common TD1 mutation of S249C in which a new cystein residue is introduced in various locations of the extramembranous subunit of the fibroblast growth factor receptor 3.

An advanced paternal age effect was reported by Lemyre et al in 1999.[5] The father of our proband was aged 48 at time of fetal conception. The significance of this is unknown at present. It is worth noting that achondroplasia in which mutation is also found in *FGFR3*, is also associated with increased paternal age.[6] More collaborative epidemiological data analysis is needed to draw such conclusion.

With modern days obstetrics care, full term thanotophoric dysplasia is less commonly seen. Unassisted neonates usually die within hours or days due to respiratory insufficiency. Survival is rare and has been reported in TDs with intensive medical intervention.[1] This prolonged suffering is not limited to the neonate concerned but also to their parents as the surviving neonates are almost always ventilator-dependent and mentally deficient.

Major differential diagnoses to TD1 include severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) in which the radiographic signs look similar to TD1 but is compatible with prolonged survival beyond neonatal period. This is understandable because it is caused by specific missense mutation lys650met in the same gene and is in the critical region of the tyrosine kinase domain activation loop of *FGFR3*. The same strongly activating mutation is also known to cause TD1. This codon lys650 also participated in another missense mutation lys650Glu (A1948G) in causing TD2.

Bone changes in achondroplasia look similar to TD but much milder than TD1. Both conditions have mutations in *FGFR3*. G380R mutation at nucleotide 1138 (G1138A or G1138C) of achondroplasia has one of the highest spontaneous germline mutation rates in human genome. Radiographic severity of homozygous achondroplasia born to two achondroplasia parents is somewhere between the most severe end of TD1 and the milder end of heterozygous achondroplasia.

TD1 and TD2 are diagnosed prenatally or in the immediate newborn period. Both subtypes are considered lethal skeletal dysplasias. For this, diagnosis is usually straight forward. Correct diagnosis allows proper genetic counselling and prognostication.

Without proper genetic counselling, most families having had a fetus with thanatophoric dysplasia would be too worried to have further pregnancy. Since the majority of cases occur sporadically, it is important to counsel that the recurrence risk is low for only one previously affected fetus, and that the extended family members of the proband are not at increased risk. To relieve parental anxiety in such low risk couple, prenatal ultrasound examination may be offered in subsequent pregnancies to identify features suggestive of TD, such as macrocephaly, vertebral ossification defect, bowed femori, micromelia, and small thorax with protuberant abdomen. If indicated, amniocentesis may be offered, and diagnosis be made by molecular analysis.

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