A CASE STUDY OF THANATOPHORIC DYSPLASIA TYPE 2

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ABSTRACT

During the last decade, the incidence of major and minor congenital anomalies in the Gaza Strip has notably increased. We report a case of thanatophoric dysplasia in a 38-week gestation newborn from Palestine. The baby had hypotonia, a large head with a prominent forehead, a wide anterior fontanel, a depressed nasal bridge, hypertelorism, a narrow chest, normal trunk length, a distended abdomen, small limbs with extra folds of skin on the arms and legs, and abnormally short fingers and toes. Radiological investigations showed flattened vertebral bodies, a short cranial base, hypoplasia of the pelvic bones, and straight long femoral bones. A possibility of a link with environmental factors (related to the recent wars in the Gaza Strip) leading to gene mutation has been suggested.

Keywords: Thanatophoric dysplasia, flattened vertebral bodies, hypertelorism, Gaza Strip

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INTRODUCTION

Thanatophoric dysplasia (TD) is the most common form of skeletal dysplasia known to be lethal in the neonatal period. The term thanatophoric is Greek for "death bearing". Infants with TD are usually stillborn or die shortly after birth from respiratory failure; however, a few affected individuals have survived into childhood with extensive medical help. TD is characterized by notably short limbs, a disproportionately small ribcage, and redundant skin on the person's arms and legs. The incidence of TD is 1 per 20,000–50,000 births. TD type 1 (TD1) is the more common form, usually caused by R248C and Y373C mutations in the fibroblast growth factor receptor 3 (FGFR3) genes. The appearance of TD1 includes the typical "telephone receiver" shape of the femur, along with frontal bossing and midface hypoplasia, but no cloverleaf skull deformity[1–3].

TD type 2 (TD2) is usually caused by K650E mutation in the FGFR3 gene. The femurs are typically straight with flared metaphyses. The most specific feature of TD2 is the cloverleaf skull, a trilobed appearance of the skull in the coronal plane that results from premature craniosynostosis of the lambdoid and coronal sutures[4].

TD1 and TD2 are autosomal dominant conditions, caused by mutations in the FGFR3 gene. This gene provides instructions for making a protein that is involved in the development and maintenance of bone and brain tissue. TD has many phenotypic similarities with homozygous achondroplasia, but the latter is distinguished by a positive family history in which both parents have achondroplasia (heterozygous for the specific FGFR3 mutations associated with achondroplasia)[5–8]. People with TD are not known to have had children. The disorder must, therefore, have not been passed between generations[9].

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CASE REPORT

Our subject was delivered to a healthy gravida 5 mother, who had two first trimester abortions after her first baby. The family has two healthy girls and no history of congenital anomalies. The parents are first-degree cousins and live in the eastern region of Gaza City. At six months

of gestation, an antenatal ultrasound scan showed that the fetus had short limbs. The delivery was at the central maternity unit at the Shifa Hospital, Gaza, by cesarean section (CS) due to a previous CS. The baby's condition was good at birth; her Apgar score at 1 and 5 minutes was 7 and 8, respectively. Birth weight was 2,100 grams (just below 3rd percentile), length 36 cm (below 3rd percentile), head circumference 34.5 cm (above 50th percentile), chest circumference 26 cm, and abdominal circumference 36 cm.

On physical examination, the baby was found to have macrocephaly, a large anterior fontanel, a prominent forehead, proptosis, hypertelorism, a depressed nasal bridge, a small chest, micromelia with redundant skin, a protruding abdomen (Figure 1), a brachydactyly hand configuration (Figures 2, 3), hypotonia, and normal external female genitalia. The results of the brain and abdominal ultrasound scans were normal. A skeletal survey (Figure 4) showed small proximal portions of the long limbs giving a rhizomelic appearance, a small chest, straight femur and humerus, hypoplastic iliac bone, and platyspondyly. These clinical features are consistent with TD2.

Figure 1. Macrocephaly, large anterior fontanel, prominent forehead, proptosis, hypertelorism, depressed nasal bridge, small chest, micromelia with redundant skin, and protruding abdomen

Figure 2. Brachydactyly hand configuration

Figure 3. Brachydactyly hand configuration

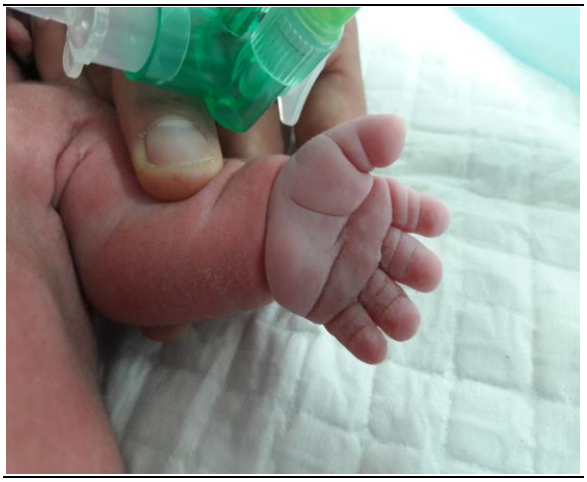
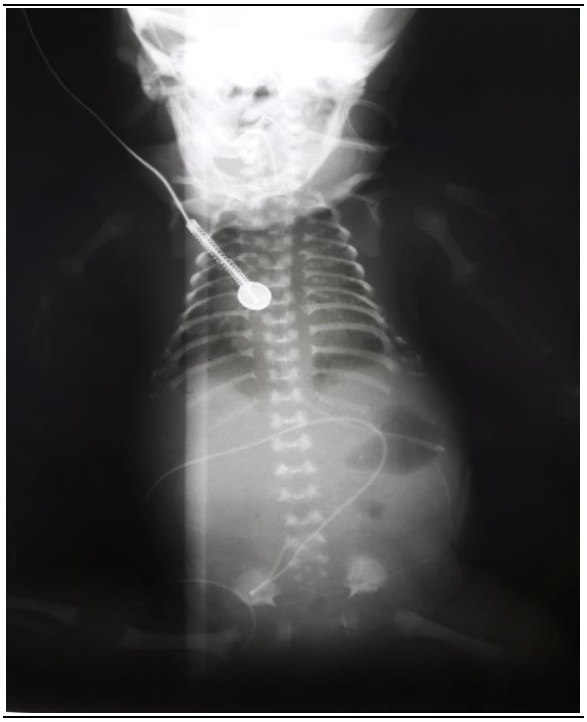


Figure 4. Small proximal portions of long limbs giving a rhizomelic appearance, small chest, straight femur and humerus, hypoplastic iliac bone, and platyspondyly



At the age of 10 minutes, the baby had significant tachypnoea with a respiratory rate of 80–90 per minute; the oxygen saturation in air was 80–85%. Therefore, the baby was intubated and ventilated at the age 20 minutes. Persistent pulmonary hypertension was evident as the baby needed 100% FiO_2 to attain an oxygen saturation of 88–89%. An echocardiography showed normal heart structure and confirmed the persistent pulmonary hypertension, which was managed using intravenous magnesium sulfate and oral sildenafil according to the local protocol. With this intensive management, the baby maintained oxygen saturation at 90–95%. Nasogastric feeding commenced on the second day. At the age of four days, the baby was still on a high mechanical ventilation setting. The baby's condition deteriorated and, despite intensive management, she died at the age of four days due to hypoxia and severe persistent pulmonary hypertension.

DISCUSSION

The clinical features of this case, including the physical findings and radiological abnormalities, are consistent with TD2. There was no family history of inherited congenital anomalies, which suggests that this is a new genetic mutation. The family resided in the eastern region of Gaza City, which had been exposed to three wars in the last decade. Studies after the wars showed a significant increase in the incidence of congenital anomalies as well as a high level of heavy metal in fetuses with congenital anomalies and their mothers [10, 11].

Unfortunately, there are no resources in the Gaza Strip for genetic testing, and the parents could not afford genetic studies in a private laboratory due to financial constraints.

CONCLUSION & RECOMMENDATION

The incidence of fatal congenital anomalies notably increased after the recent three wars in the Gaza Strip. TD is among the many rare congenital anomalies that was observed and reported in the Gaza Strip after the wars. Therefore, the possibility of a link with environmental factors leading to gene mutation has been suggested. More research and studies in this field are needed to explore this association. Unfortunately, owing to inadequate resources and research facilities as well as unavailability of genetic laboratories, we cannot confirm the diagnosis of most conditions. Having facilities for genetic studies in Gaza will not only promote research but also help in providing appropriate genetic counseling for parents. This may contribute to a decrease in the incidence of congenital anomalies.

Additional resources and a skilled staff to deal with genetic and congenital conditions in the Gaza Strip will ensure a structured team approach to these conditions. Establishment of appropriate facilities will lead to accurate diagnosis, management, documentation, and data collection. Additional resources will also promote research in this field, increasing our understanding of the link between genetic and environmental causes and, hence, contribute to the prevention of genetic and congenital conditions. The government in Gaza has no resources for appropriate investment in this field, as this is not considered a priority. Owing to economic constrains and the siege in Gaza, support from non-governmental organizations is required.

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