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ORIGINAL ARTICLE

Thanatophoric Dysplasia and the Brain—A Perinatal Pathology Study

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Abstract The purpose of this article is to analyse all cases of thanatophoric dysplasia and document the associated CNS anomalies. A retrospective study of all cases of thanatophoric dysplasia diagnosed in the department of perinatal pathology from January 2009 to December 2016. The various associated findings with due reference to the CNS manifestations were analyzed. During the study period, 7741 foetal autopsies were done, of which 24 (0.31%) were diagnosed to have thanatophoric dysplasia. The brain of one case was autolysed and hence, this had been excluded from this study. Of the 23 cases, 19 were of type 1 (83%) and 4 were of type 2 (17%). CNS anomalies were present in all. In our series, the characteristic findings seen in TD type 1 were enlarged skull, short neck, narrow thorax, protuberant abdomen, severe rhizoacromelic shortening of all four limbs with bowing of lower limbs. Whereas, type 2 manifested with large clover leaf skull with frontal bossing, short neck, short ribs, protuberant abdomen, severe rhizoacromelic shortening of all four limbs. Both the types had their characteristic fetogram findings. Central nervous system anomalies were seen in all 23 cases; which were multiple bilateral clefts seen in the inferior surface of the temporal lobe and medial surface of the occipital lobe. There were no noticeable differences in CNS abnormalities between TD type I and II. Clefting disorders consistently seen in the present series and in other reports calls for attention to be given to cortical malformations of the temporal lobe. This constellation of brain abnormalities needs recognition in fetal imaging and we propose that this should be included in the guidelines for diagnosis of thanatophoric dysplasia.

Keywords Thanatophoric dysplasia · Clefting abnormalities · Lethal skeletal dysplasia · Clover leaf skull

Abbreviations

FGFR	Fibroblast growth factor receptor
CNS	Central nervous system

Introduction

Thanatophoric dysplasia, also called as thanatophoric dwarfism, was discovered in 1967 by Pierre Maroteaux and his co-workers who used the Greek term "thanatophoric" meaning "death-bringing" [1]. Thanatophoric dysplasia is the most common skeletal dysplasia where survival beyond the neonatal period is rare. This lethal skeletal dysplasia is characterized by disproportionate small rib cage, extremely short limbs and folds of extra skin on the arms and legs. Other signs of the disorder include a narrow chest, underdeveloped lungs, and an enlarged head with a large forehead and a prominent wide-spaced eyes [2, 3] (Fig. 1). It is divided into two clinically defined subtypes [4].

- Type 1 is characterized by micromelia, bowed femur, rounded proximal femora with ragged metaphysis (telephone femora), short, broad and straight tubular

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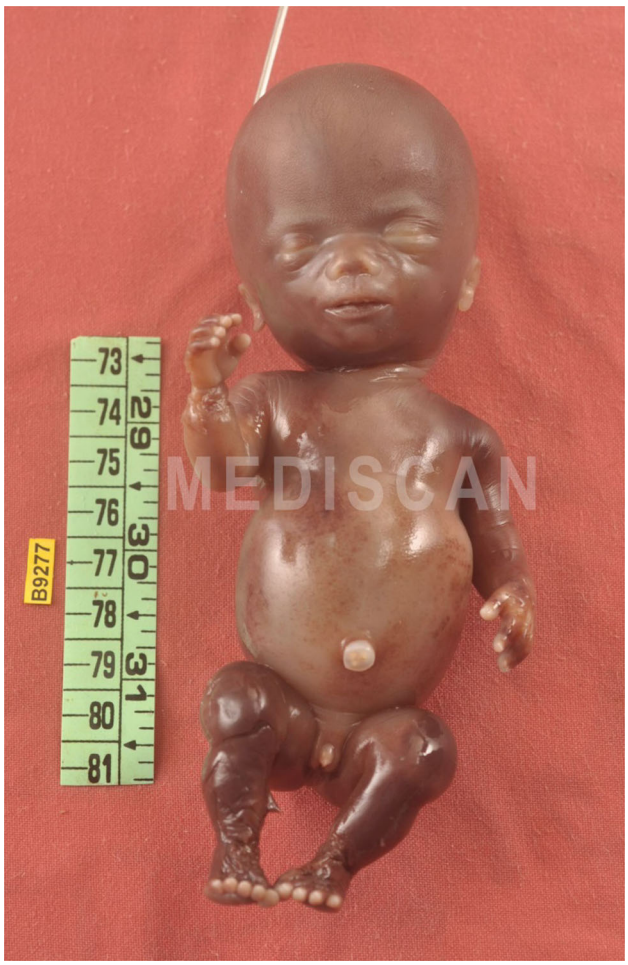

Fig. 1 Image of foetus with thanatophoric dysplasia following termination of pregnancy (gestational age 17 weeks)

bones, uncommonly cloverleaf skull and flattened vertebral bodies with central depression (Fig. 2).

- Type 2 is characterized by micromelia with short broad and straight long bones femur and uniform presence of moderate to severe cloverleaf skull deformity, flattened vertebral bodies with irregular upper and lower plates [3, 5] (Fig. 3).

Some features common to both the types are micromelia, short ribs, narrow thorax, macrocephaly, distinctive facial features, brachydactyly, redundant skin folds, hypoplastic iliac bones, unossified pubic bone, and narrow sacrosciatic notch.

The characteristic fetogram findings in the telogram are proximal portions of the long limbs which are small giving a rhizomelic appearance, long limbs (typically humeri and femora) have a typical "telephone handle" (type 1) bowing with metaphyseal flaring, usually hypoplastic ilium, small squared iliac wings, may show a "trident" acetabular roof, narrow chest, short horizontal ribs, small scapulae, relative macrocephaly, frontal bossing, proptosis, nasal

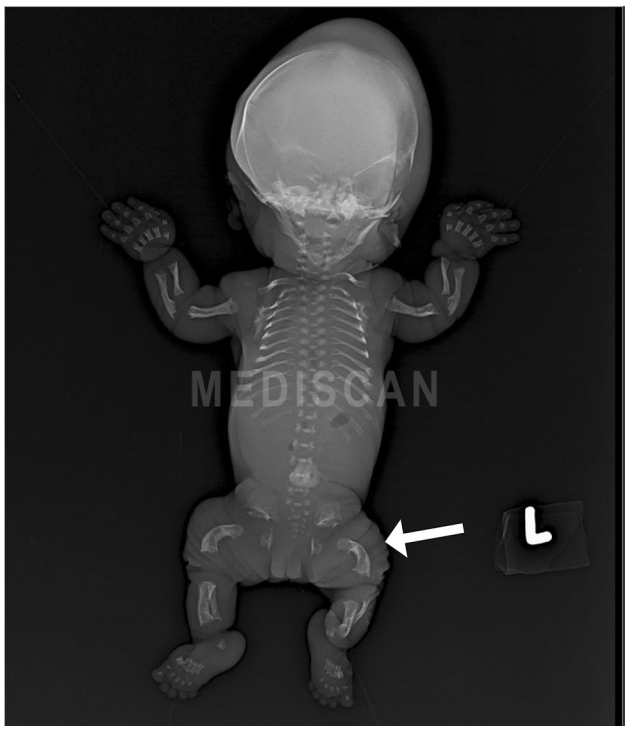

Fig. 2 Anterior posterior view fetogram of fetus with type 1 thanatophoric dysplasia (gestational age 25 weeks). Note the telephone femora marked with arrow

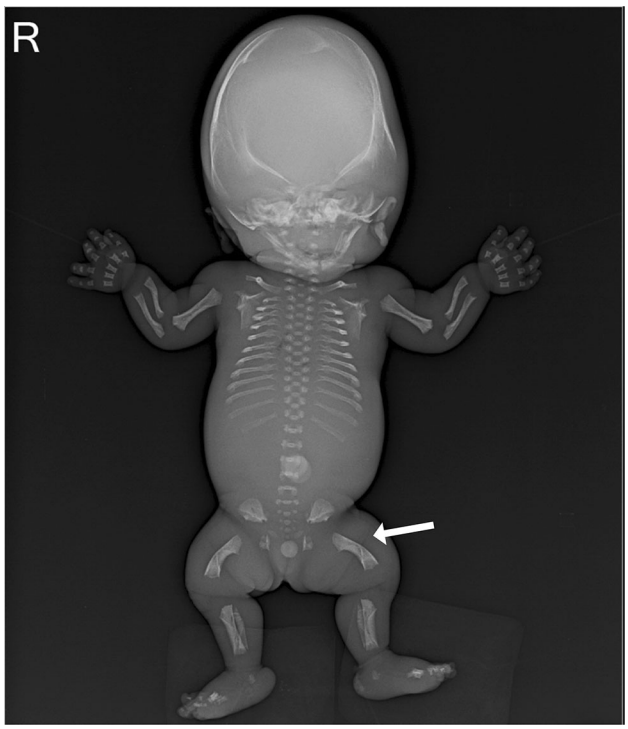

Fig. 3 Anterior posterior view fetogram of fetus with type 2 Thanatophoric dysplasia (gestational age 23 weeks). Note the absence of telephone femora

bridge, cloverleaf skull (with type II), platyspondyly (flattening of vertebral bodies), and normal trunk length.

Etiopathology

The FGFR3 is a receptor comprised of three domains: an extracellular ligand-binding (consisting of three immunoglobulin like sub domains), a transmembrane domain and an intracellular domain (consisting of two tyrosine kinase sub domains) [6].

In thanatophoric dysplasia type I, cysteine replaces several amino acids in three separate regions in the extracellular domain [7]. These mutations cause the activation of the receptor. It is interesting to remark that if cysteine replaces amino acids located in different places, this also causes different intensities of activation, producing less severe form of dwarfism, like achondroplasia. This suggests that the intensity of FGFR3 activation is position-dependent [8]. In thanatophoric dysplasia type II, lysine is substituted by glutamic acid in one of the intracellular sub domains of FGFR3 [9]. FGFR3 is the only gene in which mutation is known to cause thanatophoric dysplasia.

The inheritance of thanatophoric dysplasia is considered an autosomal dominant disorder. The gene, FGFR3, is mapped to the short-arm of chromosome 4(4p16.3). Penetrance of this mutation is 100%. Virtually all cases of thanatophoric dysplasia are caused by de-novo mutations in the FGFR3 gene. No affected individuals are known to have had children; therefore, the disorder has not been passed to the next generation [8].

Materials and Methods

A retrospective study of all cases of thanatophoric dysplasia diagnosed in the department of perinatal pathology for duration of 8 years from January 2009 to December 2016. The diagnosis of thanatophoric dysplasia was made based on its characteristic morphological, radiological and histopathological findings. The various associated findings with due preference to the CNS manifestations were analyzed.

Results

During the study period, 7741 fetal autopsies were done, of which 24 (0.31%) were diagnosed as thanatophoric dysplasia. In one of the cases with type 2 thanatophoric dysplasia, the brain was autolyzed and could not be commented on. Hence, this case was not included in this series. Of the 23 cases, 19 were Type 1 (83%) and 4 were type 2 (17%). CNS anomalies were present in all 23 cases.

In our series, the characteristic findings seen in thanatophoric dysplasia type 1 were enlarged skull, short neck, narrow thorax, protuberant abdomen, severe shortening of all four limbs with bowing of lower limbs. Fetogram findings were long bones-short broad and bowed with flaring and metaphysical cupping (telephone receiver femora), shortened metacarpal and metatarsals, platyspondyly with 'H' shaped vertebral spaces, narrow thorax, large normally mineralised vault.

Whereas, type 2 manifested with large clover leaf skull with frontal bossing, short neck, short ribs, protuberant abdomen, severe shortening of all four limbs. Fetogram findings were short long bone with overtubulation, femur was short with metaphysical irregularity without bowing, square ileum with narrow sciatic notch, narrow thorax, shortened metacarpal and metatarsals, spine with severe platyspondyly.

Central nervous system anomalies were seen in all 23 cases, which included multiple bilateral clefts in the inferior surface of the temporal lobe and medial surface of the occipital lobe (Figs. 4, 5). Two fetuses had dandy walker malformation with inferior vermian agenesis of which one also had ventriculomegaly. Both the cases with dandy walker malformation was of type 2 thanatophoric dysplasia. One fetus had an extra renal pelvis. The commonly noted other features were depressed nasal bridge, bulbous nose, high forehead, low set posteriorly rotated ears. Clefting abnormality were seen in all cases irrespective of the types of thanatophoric dysplasia. One fetus had an omphalocele.

Histopathologicaly, the resting cartilage is unremarkable. The endochondrial ossification shows very severe but non-specific disturbance characterized by marked retardation of the growth zone with disorderly proliferative and hypertrophic chondrocytes. The cartilaginous spicules in the metaphysis are reduced in number, small and distorted. Histopathology of brain also shows abnormal sulci (Fig. 6).

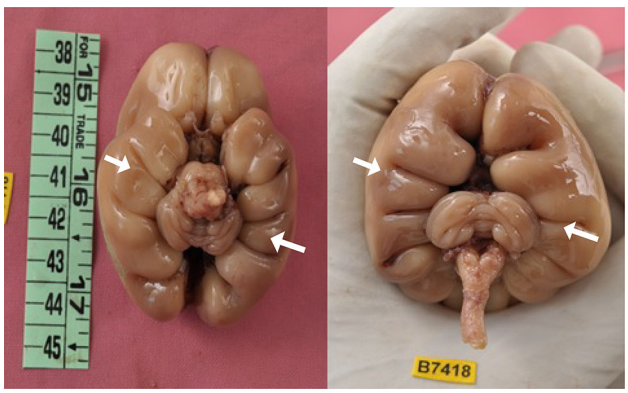

Fig. 4 Inferior and dorsal view of the brain of fetus with Thanatophoric dysplasia demonstrating multiple clefts (gestational age 21 weeks)

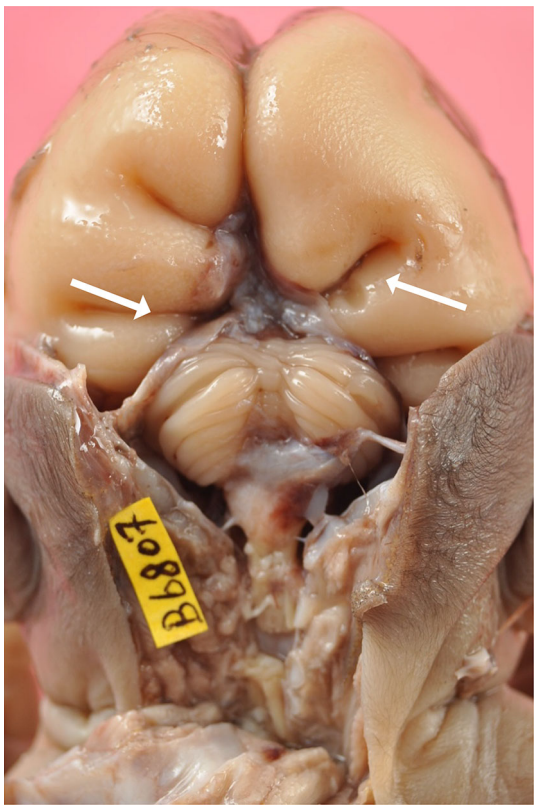

Fig. 5 Brain of fetus with Thanatophoric dysplasia (gestational age of 20 weeks). Posterior parietal and occipital lobes with clefts

Discussion

In Potter's series of 25 cases, the central nervous system malformations noted were megalencephaly and abnormal pattern of temporal lobes. It was noted that megalencephaly if present was always associated with abnormal surface configuration of prominent temporal lobes. One of the early reports of neuropathological findings in thanatophoric dysplasia were described by Goutieres et al. in 1971, where abnormalities of the temporal lobe gyri, hippocampal dysplasia, and polymicrogyria were seen in the temporal cortex of two infants.

Chang et al. (1984), a neuropathological study of eight cases of thanatophoric dysplasia have reported abnormalities including hypoplasia of posterior fossa, megalencephaly, cerebral gyral disorganization, hippocampal malformation, neuronal heterotopia, nuclear dysplasia, and abnormal axonal bundles. There are no noticeable differences in CNS abnormalities between thanatophoric dysplasia with and without cloverleaf skull [10]. Miller et al. [11] have stated that it is important to assess the brains of fetuses with suspected thanatophoric dwarfism because the presence of associated brain malformations can assist in the antenatal diagnosis and accurate counselling of patients. Noronha et al. [12] in report of 2 cases of thanatophoric dysplasia have reported that both cases revealed temporal lobe polymicrogyria, abnormalities of the hippocampus and heterotopic neuroglial tissue within the meninges.

There were no noticeable differences in CNS abnormalities between thanatophoric dysplasia type I and II. In our series of 12 cases of thanatophoric dysplasia, which is the largest perinatal pathology series reported from a single center, the clefting defect of the temporal lobe was seen in all cases. These observations suggest that CNS abnormalities are a characteristic and distinct manifestation of thanatophoric dysplasia.

Though central nervous system abnormalities have been recognized, these are not widely recognized in fetal imaging. The typical temporal lobe enlargement and abnormal sulcation that are deemed pathognomonic of thanatophoric dysplasia which are consistently found at autopsy are not commonly described in the literature on prenatal imaging of skeletal dysplasia. The standard axial views of the brain are limited for diagnosis of temporal brain abnormalities but can identify the presence of increased number of deep sulci in the temporal regions [13]. The anterior and mid coronal plane images are certainly of great use when attention is paid to the temporal lobes for identification of the increase in size of these lobes as well as the marked deep sulcation [14]. Although imaging these ultrasound planes do help in the diagnosis,

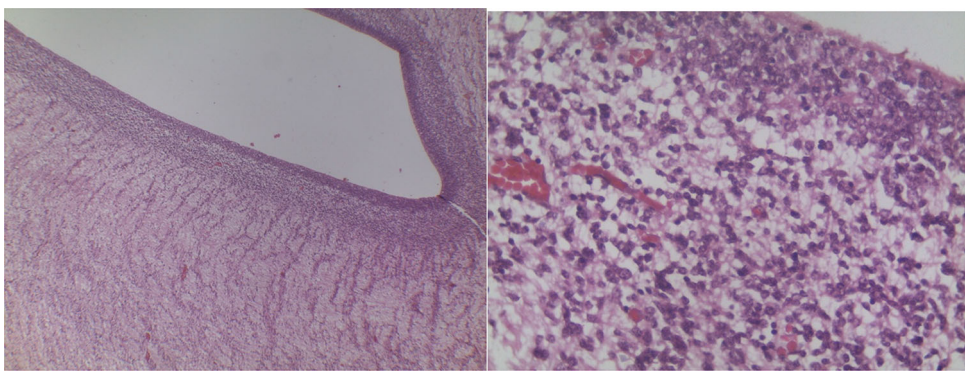

Fig. 6 Histopatholgy of brain of fetus with Thanatophoric dysplasia. Image on left shows deep abnormal sulci with outer layer of neurons and inner layer of glial fibres. Image on right is a power photomicrograph of the same area both stained with haematoxylin and eosin

but the expertise of the operator, fetal position and maternal body habitus are factors that influence diagnosis.

Conclusion

Clefting disorders consistently seen in the present series and in other reports calls for attention to be given to cortical malformations of the temporal lobe. Knowledge of these abnormalities in the brain can be used to refine the antenatal diagnosis of skeletal dysplasia, which is often a great challenge in clinical practice. This constellation of brain abnormalities needs recognition in fetal imaging and we propose that this should be included in the guidelines for diagnosis of thanatophoric dysplasia.

Compliance with Ethical Standards

Ethics Approval Clearance obtained—Reg No. ECR/214/Indt/TN/2014.

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