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Case Report

Incidence of Skeletal Dysplasias in North Coastal Andhra Pradesh

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ABSTRACT
Skeletal dysplasias are a diverse group of diseases primarily affecting the development of the osseous skeleton. They manifest with disproportionate short stature, malformations, and/or deformations and range from relatively mild to severe and lethal conditions. Thanatophoric dysplasia (TD) is the most common form of skeletal dysplasia that is lethal in the neonatal period. The term, thanatophoric, derives from the Greek word thanatophorus, which means "death bringing" or "death bearing." Phocomelia is a type of Meromelia, in Meromelia there is partial agenesis of limb buds. Four limb Phocomelia is a severe combination of limb defects in which total or partial agenesis of upper and lower limbs is seen. Short rib polydactyly (SRP) syndrome is a group of lethal neonatal skeletal dysplasias of autosomal recessive inheritance, characterized by markedly narrow ribs, micromelia and multiple anomalies of major organs. Dwarfism syndromes are complex, heterogeneous, and generally rare. Most of the radiologists are familiar with achondroplasia, as the most common short-limbed dwarfism syndrome are a variety of syndromes with rhizomelic type, proximal shortening of humerus or femur. Incidences of all the above dysplasias are common in north coastal Andhra pradesh.

Key Words: Dwarf, Dysplasia, Rhizomelia, Thanatophoric, Short-Rib

INTRODUCTION

Skeletal dysplasias are a diverse group of diseases primarily affecting the development of the osseous skeleton. They manifest with disproportionate short stature, malformations, and/or deformations and range from relatively mild to severe and lethal conditions. To date there are over 250 unique and well-characterised skeletal dysplasias, many of which can be grouped into different diagnostic groups and/or bone dysplasia families based on clinical similarities (Francomano et al 1996). Many skeletal dysplasia phenotypes are characterized by severe deformations and/or malformations of numerous skeletal elements and with such conditions it is sometimes easy to overlook other clinical aspects, such as the effect these skeletal abnormalities may have on the soft tissues of the body (Mogayzel, 2001). The rapid growth in knowledge has resulted in a complex new terminology. Two international meetings have been held, the first in 1969 Paris (Sillence *et al.*, 1979) the second in 1977 (International nomenclature of constitutional diseases of bone 1978) held at Paris to formulate an acceptable nomenclature for constitutional disorders of bone. The second international nomenclature divided the skeletal dysplasias into five major groups: osteochondrodysplasias, i.e., abnormalities of cartilage and/or bone growth and development; dysostoses, *i.e.*, malformations of individual bones, singly or in combination; idiopathic osteolyses, i.e., conditions associated with resorption of bone and with secondary abnormalities; chromosomal aberrations with unusual skeletal abnormalities; and primary metabolic abnormalities, a large group of conditions where the pathogenetic mechanism is known or a biochemical defect has been demonstrated. The terminology for many of the dysplasias has been based upon that part of the skeleton that is affected in radiographs. Thus, dysplasias which demonstrate significant epiphyseal, metaphyseal, or diaphyseal abnormalities are called epiphyseal, metaphyseal, or diaphyseal dysplasias, respectively. Some dysplasias are named for the segment of the limbs that shows the shortening, e.g., rhizomelic (proximal), mesomelic (middle), and acromelic (distal) dysplasias.

Classification of constitutional diseases of bone in the Second international nomenclature (May 1977) showing following abnormalities of cartilage and/or bone growth development Identifiable at birth:

I. Achondrogenesis type i (parenti-fraccaro)

II. Achondrogenesis type ii (langer-saldino)

III. Thanatophoric dysplasia

IV. Thanatophoric dysplasia with cloverleaf skull

V. Short-ribpolydactyly syndrome type i (saldino-noonan) (perhaps several forms)

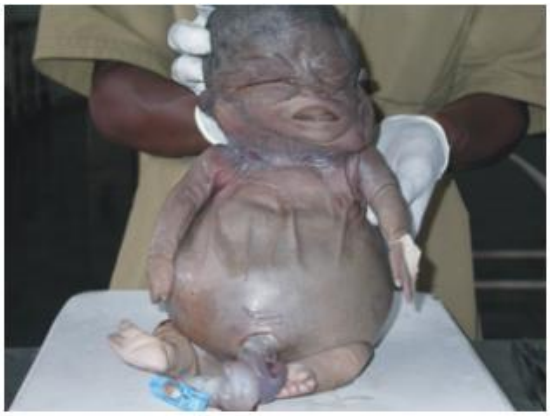

Fig.1. Flat face and depressed nasal bridge with protuberant abdomen

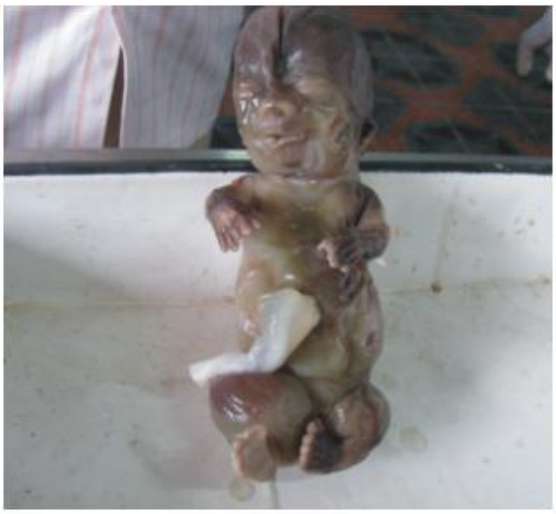

Fig.4. Showing shortening of all the four limbs

Fig. 7. Cleft lip and palate with polydactyly

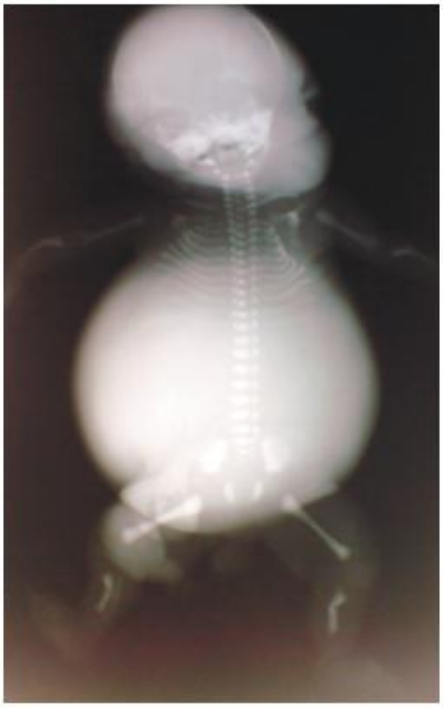

Fig.2. Radiographic picture of thanato-photic dysplasia

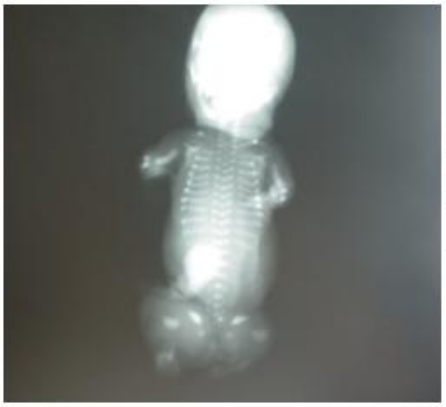

Fig. 5. Radiograph of phocomelia foetus

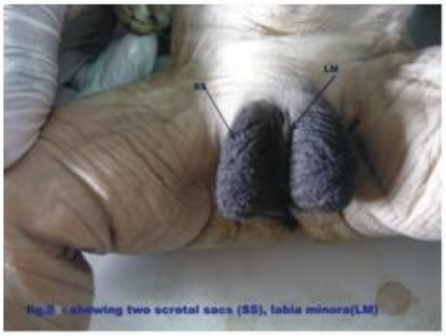

Fig. 8. Ambiguous genitalia

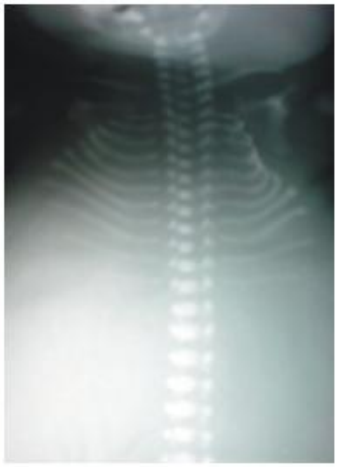

Fig.3. Flat vertebral bodies and asymmetric ribs

Fig. 6. Skiagram of SRPS foetus

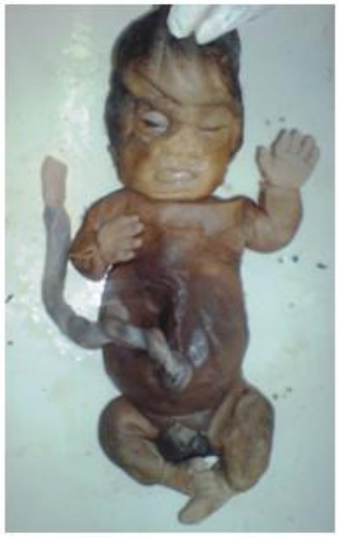

Fig. 9. Foetus with achondroplasia

VI. Short-ribpolydactyly syndrome type ii (majewski)
VII. Chondrodysplasia punctata
VIII. Campomelic dysplasia
IX. Other dysplasias with congenital bowing of long bones (several Forms)
X. Achondroplasia
XI. Diastrophic dysplasia
XII. Metatropic dysplasia (several forms)
XIII. Chondroectodermal dysplasia (ellis-van creveld)
XIV. Asphyxiating thoracic dysplasia (jeune)
XV. Spondyloepiphyseal dysplasia congenita
XVI. Kniest dysplasia
XVII. Mesomelic dysplasia
XVIII. Acromesomelic dysplasia
XIX. Cleidocranial dysplasia
XX. Larsen syndrome
XXI. Otopalatodigital syndrome

Thanatophoric dysplasia (TD) is the most common form of skeletal dysplasia that is lethal in the neonatal period. The term, thanatophoric, derived from the Greek word *thanatophorus*, which means "death bringing" or "death bearing." Thanatophoric dysplasia is divided into 2 clinically defined subtypes: thanatophoric dysplasia type I (TDI or TD1) and thanatophoric dysplasia type II (TDII or TD2). The clinical subtypes of thanatophoric dysplasia are defined by the curved or straight appearance of the long bones. TDI, the more common subtype, is characterized by a normal-shaped skull and curved long bones (shaped like a telephone receiver); the femurs are most affected. TDII is associated with a clover leaf-shaped skull and straight femurs. However, clinical overlap is observed between these subtypes. TDI and TDII are caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene, which has been mapped to chromosome band 4p16.3 (Defendi, 2009)

Case report: A 29 year old female was asked to get her ultrasound scanning during 28weeks of gestation. Scan revealed a male foetus with abnormal shortening of limbs and protruberant abdomen. Pregnancy was terminated at the same gestational age. The still born foetus was brought to the department of anatomy, MIMS medical college as a part of the project work.The external features included a Macrocephalic head with frontal bossing with a circumference of 40 cms, Flat facies with depressed nasal bridge, malformed and low set ears, webbing of the neck, a narrow thorax with a protuberant abdomen (Fig. 1), postaxial polydactyly of both hands. Marked bilateral shortening of the limbs (micromelia) with redundant skin folds. Radiographic picture showed translucent upperlimb bones. Femorae were normal with bowing of tibia (Fig. 2). The veretebral bodies were small and flat with wider intervertebral space and asymmetric arrangement of costae (Fig.3).

Roberts Tetraphocomelia

Phocomelia is a type of Meromelia, in Meromelia there is partial agenesis of limb buds. Four limb Phocomelia is a severe combination of limb defects in which total or partial agenesis of upper and lower limbs is seen; leading to the proximity of limbs to the trunk of the foetus resembling the flippers of a seal "an aquatic animal". Such babies are termed as Thalidomide babies attributing dysmorphogenesis of limb buds to this drug.

Case report: A 27 year old female during her routine antenatal checkup was advised an obstetric scan in the fifth month of gestation. Ultrasound scan revealed Phocomelia. There is no history of consanguity amongst the parents and no history of drug intake during first trimester available; earlier female child is healthy. The foetus of the present study showed shortening of both upper and lower limbs (Fig.4). Radiograph of foetal cadaver was taken and foetal autopsy was performed.

Axial skeleton: cranial and facial bones were normal, ribs were short and straight, the vertebral column was normal, the pelvis showed underdeveloped bones. The appendicular skeleton deformities included bilateral short and bowed humerus, forearm bones (radius &ulna) were partially formed which resulted in a typical phocomelia; both lower limbs had short femurs, bowing of tibia and absence of fibula on both sides (Fig.5). Other systems had no detected abnormalities.

Short Rib-Polydactyly Syndrome (SRPS)

Short rib polydactyly (SRP) syndrome is a group of lethal neonatal skeletal dysplasias of autosomal recessive inheritance, characterized by markedly narrow ribs, micromelia and multiple anomalies of major organs. (Lorraine 1986). Classically, four different types have been described: SRPS I (Saldino-Noonan); SRPS II (Majewski); SRPS III (Verma-Naumoff); and SRPS IV (Beemer-Langer). The following are typical of the type II (Majewski's syndrome): narrow, constricted thorax; short ribs; dwarfism; micromelia; polydactyly; enlarged head; depressed nasal bridge; cleft upper lip (Johannes *et al.*, 1993).

Short-rib polydactyly syndrome has been known for its rarity. Only 100 published cases have been noticed so far Mastroiacovo *et al.*, (1990). After routine dissection, macroscopic observations are noted.

Case report: Postmortem radiography revealed normal vertebral bodies that appeared square, with extremely short ribs. There is generalized shortening of all long bones (Fig. 6). The skull, clavicles and pelvis appeared

normal. The metaphyseal ends are smooth. At autopsy, the foetal weight recorded 2,500 grams with a crown-rump 41cms.

The foetus showed a relatively large head and a long trunk with micromelia. The external features included a bulging forehead with a circumference of 39.5 cms, depressed nasal bridge, malformed and low set ears, a right paramedian cleft upper lip, a narrow thorax, postaxial polydactyly of both hands and feet (Fig.7).

External genitalia - a rudimentary phallus, undescended testes present in the scrotal sacs that are unfused near the root of scrotum, labia minora with a vestibule, an atretic vaginal canal (fig.8).

Achondroplastic Dwarf

Dwarfism syndromes are complex, heterogeneous, and generally rare. Achondroplasia is caused by a mutation in the FGFR3 gene on chromosome 4. Achondroplasia can be diagnosed before birth by ultrasound measurements of their long bones and head size. After birth, the diagnosis is usually based on radiographic studies of the babies bones and head size. The radiograph images usually reveal a small skull base, shortened long bones, square-shaped long bones, and normal-sized bones in the trunk area. A baby who inherits the gene from both parents will die before birth or shortly after birth from respiratory failure (Hubpages No date). Achondroplasia is inherited as an autosomal dominant trait.If one parent has a defective gene for achondroplasia, the infant has a 50% chance of inheriting the disorder. If both parents have defective gene, the infant's chances to be affected is 75% (NCBI 2009)

Case report: Distinctive facial features, particularly a prominent forehead and underdevelopment of the nose were observed. Trunk was normal with abnormal length of upper and lower limbs (Fig. 9). Radiography revealed generalized shortening of all the appendicular bones (Fig. 10).

DISCUSSION

Thanatophoric dysplasia affects about 1 in 60,000 births (Vajo *et al.,* 2000) and is the most common lethal bone dysplasia. Infants are hypotonic with protruberant abdomens and abducted externally rotated thighs. The most typical plain film findings are pronounced flattening of the vertebral bodies, bowed extremities, and severe rhizomelic dwarfism. The disorder is uniformly fatal within hours to days after birth due to severe respiratory failure. TDI and TDII are caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene, which has been mapped to chromosome band 4p16.3 (Defendi 2009)

Phocomelia occurs due to the dysmorphogenesis of the limb buds during 4th and 5th week of gestation due to intake of the drug thalidomide. Mesomelic dysplasia is variation of Phocomelia, characterized by the shortening of the middle portions of the limbs, that is "radius, ulna & tibia, fibula" The drug Thalidomide was banned in 1960. Phocomelia is an Autosomal recessive trait, and occurs in individuals carrying single copy of gene that exhibits dyschondroosteosis. Those having two copies of the genes have mesomelic dysplasia. The causative gene for this has been discovered as SHOX gene in 1998. The gene is located on both X and Y chromosomes termed psuedo autosomal loci. The gene ESCO2 is the main gene with documented Roberts syndrome-causing mutations. It is is located on 8p21.1 locus (Gordillo, *et al.,* 2005). Furthermore, some others genes have been suspected for being responsible of Roberts syndrome (Musio *et al.,* 2004).

In 1971, Majewski and colleagues described a malformation syndrome, later defined as short rib polydactyly syndrome type II - Majewski (Johannes P 1993). All forms of the SRPS hither to described are thought to have an autosomal recessive inheritance i.e., pericentric inversion of chromosome 4. The infant in that study showed an extremely narrow chest, a protuberant abdomen, and very short limbs with pre and/or post axial polydactyly. There was also a median cleft lip or palate, hypoplasia of the epiglottis and larynx, ambiguous genitalia and renal tubular and glandular cysts (Yang 1998), Montemarano *et al.,* (1995), Shama *et al*., (1992).

Achondroplasia is basically a disorder of bone development. It is caused by a mutation in a single gene on chromosome 4 that regulates the conversion of cartilage to bone. Achondroplasia occurs in one in every 15,000 to 40,000 live births. These new mutations are more likely to occur in the sperm of fathers over 35; the mother's age does not matter, as far as is presently known. The disorder affects both sexes and all races equally.

The mammalian musculoskeletal system is a complex system of different tissues and biomechanical properties. Together these tissues enable locomotion, protect soft organs from damage, and act as a scaffold for our bodies. Early detection of an asymptomatic or a mild myopathy may lead to an earlier diagnosis of an underlying skeletal dysplasia (Bondestam *et al.,* 2007).

A total of 200 foetal autopsies have been performed so far in the last two years and these four fatal antenatal cases have been spotted which shows a higher incidence of fatal skeletal disorders in the rural population of Vizianagaram district. This does not give a total picture of the incidence of dysplasias in this area as many unreported cases might be there.

In most of the cases the defect is a genetic error which has to be further investigated and popularized, so that the preventive measures can be thought over. Gene mapping for most of the antenatal cases is to be done along with epidemiological survey.

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