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A Term Male Neonate with Achondroplasia and Persistent Pulmonary Hypertension: A Case Report

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Abstract: Achondroplasia is the most common non lethal variant of chondrodysplasia with birth prevalence of 1 in 15,000 to 40,000 births. These results from autosomal dominant inheritance although de novo mutations in the Fibroblast growth factor 3 (FGFR3) genes are responsible in majority of the cases. There exists a strong correlation between the site of mutation and the clinical phenotype. The phenotypic features of achondroplasia are often evident at birth, and the diagnosis is unparalleled. Proximal (rhizomelic) shortening of the extremities, trident hand, and midfacial hypoplasia with large head are distinct phenotypic features. Similarly there are unique radiological features like flaring and cupping of tubular bones, square shaped iliac wings with flat acetabulum and narrow caudal interpedicular distance. A 3500grams, 38weeks male neonate was born by elective c-section to a 3rd gravid. There was respiratory distress soon after birth for which the infant required ventilatory support. Antenatal ultrasound revealed polyhydramnios, rhizomelic shortening of the limbs, large head and small chest. Previous female sibling died at 24 hours of life with respiratory distress, dysmorphic facies & short limbs (probably achondroplasia) and mother also had a 2nd trimester abortion. The neonate had characteristic features of achondroplasia like proximal shortening of the limbs, excess skin creases, large head, small chest, micrognathia, short stubby fingers along with trident hand. Facial profile revealed depressed nasal bridge, hypertelorism, short tongue. The neonate had persistent pulmonary hypertension without pulmonary hypoplasia was treated for the same. The chromosomal analysis revealed common G1138A mutation in the FGFR3 located on chromosome 4p16.3. We report a term, male neonate with rhizomelic dwarfism with facial dysmorfisim suggestive of achondroplasia which was confirmed by chromosomal analysis.

Keywords: Achondroplasia, Fibroblast growth factor 3, neonate, persistent pulmonary hypertension, rhizomelic shortening, trident hand.

INTRODUCTION

Achondroplasia is the most common nonlethal variant of chondrodysplasia leading to short-limbed dwarfism. The estimated prevalence of achondroplasia ranges from 1/15,000 to 1/40,000 [1]. It is inherited as an autosomal dominant trait with complete penetrance [2, 3]. However, sporadic cases have been reported due to new mutations due to advanced paternal age [4,5].These heterozygous mutations occur in genes encoding Fibroblast growth factor 3(FGFR3) located at chromosome 4p 16.3 and Parathyroid hormone receptor(PTHR) in 80%-90% of all cases, thus leading to abnormal transmembrane receptors and cartilage formation[6,7].

The phenotypic features of achondroplasia are frequently apparent at birth, and the diagnosis is often unequivocal. The characteristic findings include proximal shortening of the extremities, trident hand, limited extension of the elbow, genu varum along with exaggerated lumbar lordosis. Typical facies consist of frontal bossing with midface hypoplasia and megalencephaly [9, 10]. The path gnomonic radiological manifestations are small cuboids vertebral bodies, lumbar lordosis coupled with progressive narrowing of the caudal (lumbar) interpedicular distance. Similarly, thoracolumbar kyphosis, anterior beaking of the first and second lumbar vertebrae. The pelvic bones in the neonate show distinctive anatomy with square shaped ilium having rounded corners and narrow greater sciatic notch. Persistent pulmonary hypertension (PPHN) in early neonatal period in achondroplasts is often associated with pulmonary hypoplasia.

CASE REPORT

A 38weeks, 3500grams male neonate was born of consanguineous marriage to a 3rd gravid by elective

c-section. The infant was admitted with respiratory distress since birth. Pre natal ultrasound at 36 weeks revealed discrepancy in fetal measurements Biparietal diameter (BPD) >95th centile, Abdominal circumference (AC) >95th centile, Femur length (FL) and Humerus length (HL) <5th centile along with polyhydramnios (max vertical pool 8 cm). There were other features like frontal bossing with depressed nasal bridge representing midfacial hypoplasia and shortened long bones. Also there was "bell-shaped" thorax with narrow chest , distended abdomen and there were no other abnormalities.

The first pregnancy was a female neonate who died within 24 hours of life with respiratory distress, dysmorphic facies and short limbs (probably achondroplasia). Also the second pregnancy was a 2nd trimester abortion. Father was 38years old, however the karyotyping of both parents was normal.

The infant required resuscitation after birth with APGAR score of 5&7 at 1min & 5mins respectively. The neonate had rhizomelic shortening of the limbs (as shown in figure 1A & 1B), excess skin creases, large head with occipitofrontal circumference of 37cms (>90th centile). Facial profile revealed depressed nasal bridge, hypertelorism, short tongue and micrognathia (as pointed in figure 1C). Chest was small (chest circumference 33cms) with short stubby fingers along with trident hand. Length of the neonate was 42cms (<10th centile). On examination, the neonate had respiratory distress with grunt and moderate to severe intercostal and sub costal retractions requiring positive pressure ventilation for a week. Although pulmonary hypoplasia was considered initially, it was ruled out as the chest x ray revealed well expanded lungs with prominent bronchovascular markings (as shown in figure 2A). However in the later course baby had clinical features of PPHN, confirmed by echocardiography which depicted dilated right atrium, right ventricle with ballooning of the inter atrial septum (as shown in figure 2B). Infantogram showed large head with narrow thorax and short tubular bones (as shown in figure 3A). X ray of the limbs depicted shortening of the humerus (rhizomelic) with cupping of the lower ends of radius & ulna (as shown in figure 3B). Similarly there was shortening of femur with cupping and flaring and relatively long fibula. (as shown in figure 3C). Also, trident hand was noted (as shown in figure 4A) and anteroposterior radiograph of lumbar spine revealed gradual narrowing of interpedicular distance from L_1 to L_5 (as shown in figure 4B).Pelvic X ray revealed square shaped ileum with flat acetabular roof(as shown in figure 4C).

The neonate received supportive and specific treatment for PPHN and was weaned off the positive pressure support a week later. The infant was started on oral feeds and was discharged in 2nd week of life. The infant chromosomal analysis revealed common G1138A mutation in the fibroblast growth factor gene3 (FGFR3) located on chromosome 4p16.3, thus confirming achondroplasia.

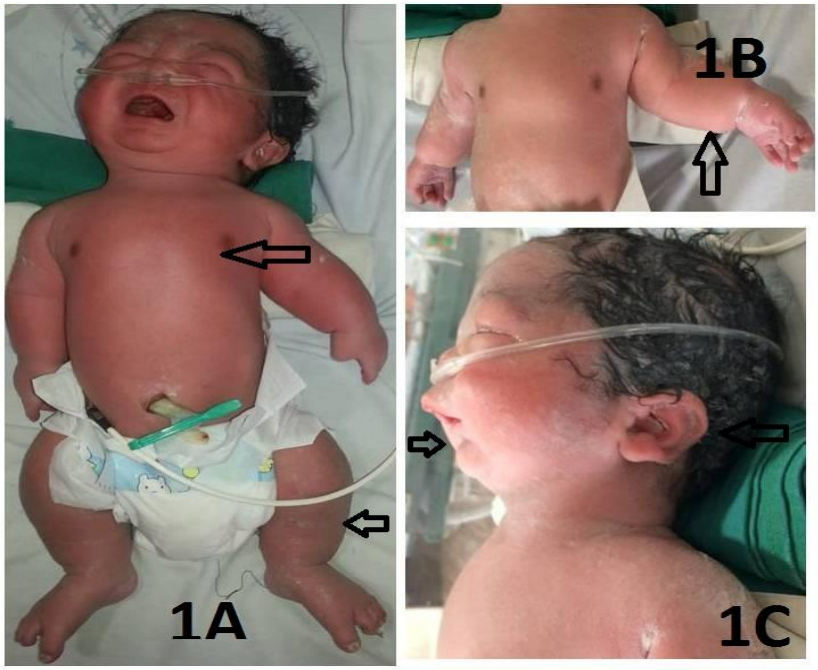

Fig 1A: Clinical photograph revealing short extremities, flat facial profile, small chest, short stubby fingers, excess skin folds

Fig 1B: Clinical photograph depicting rhizomelic shortening of limbs

Fig 1C: clinical photograph, lateral view showing low set ears, micrognathia, mid facial hypoplasia

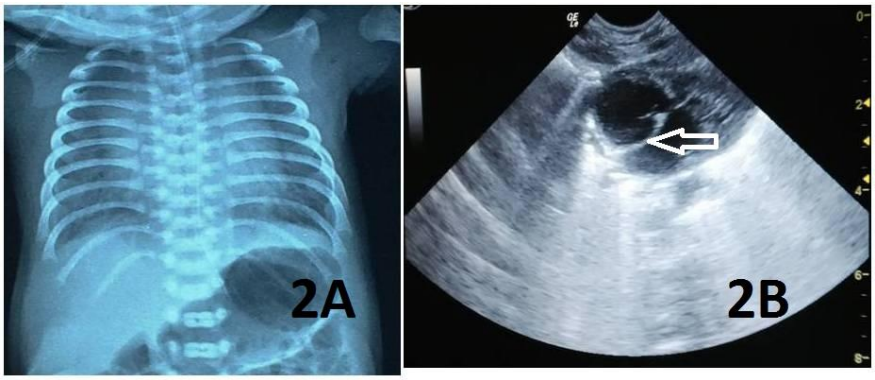

Fig 2A: Chest roentogram revealing well expanded lungs, narrow chest, prominent bronchovascular markings, tubular heart, presence of gas shadow in the stomach & intestines.
Fig 2B: Echocardiogram showing dilated right atrium, right ventricle with ballooning of the inter atrial septum

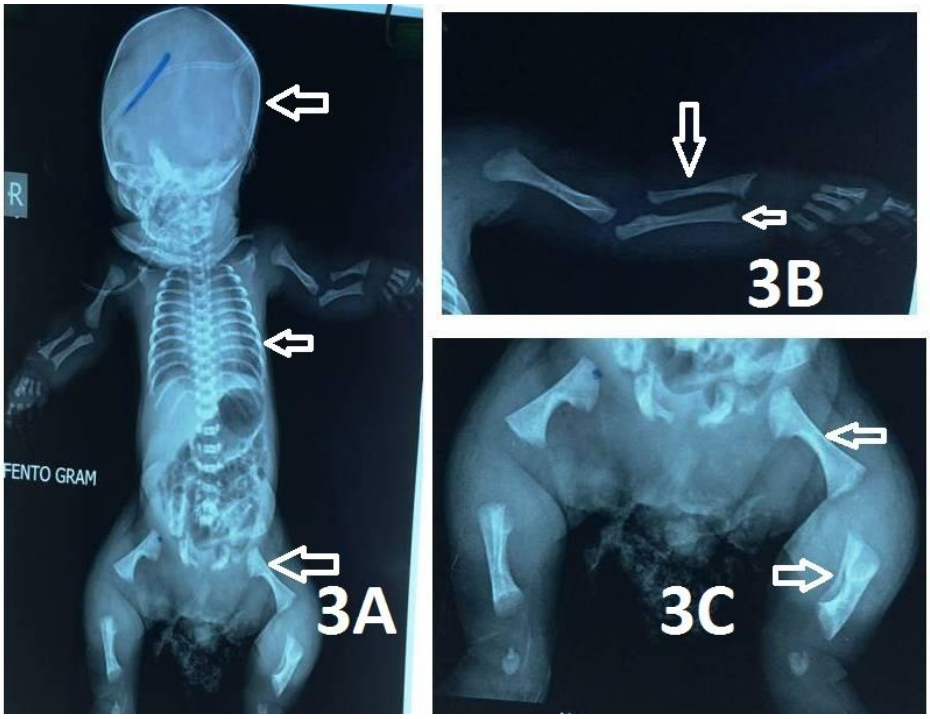

Fig 3A: Infantogram revealing large head, narrow thorax, short tubular bones
Fig 3B: X ray of the limbs showing rhizomelic shortening of the humerus with cupping of the lower ends of radius & ulna.
Fig 3C: X ray of the both lower limbs showing short femur, cupping & flaring of the metaphyseal ends, relatively normal length fibula

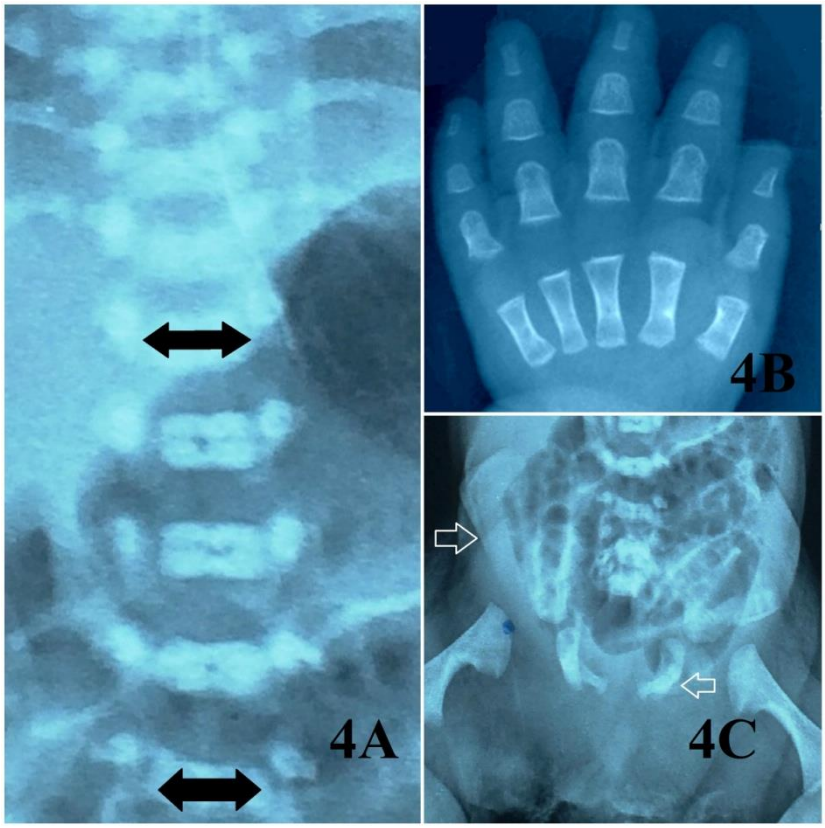

Fig 4A: X ray left hand showing trident hand (Second, third and fourth digits show equal lengths with increased spacing between the third and fourth digits)

Fig 4B: Anteroposterior radiograph of lumbar spine shows gradual narrowing of interpedicular distance from L_1 to L_5

Figure 4C: X ray pelvis revealing square shaped ileum and flat acetabular roof

DISCUSSION

The term "achondroplasia" denotes "lack of cartilage" rather than abnormal cartilage, hence a misnomer. The terms "chondrodysplasia" or "chondrodystrophy" imply abnormal cartilage tissue formation and sustenance denoting group of short-limb dwarfing conditions. In achondroplasia, there is rhizomelic shortening with the arms and thighs being involved more severely than the forearms, legs, hands, and feet as in the index infant [1, 2, 8, 9, 10].

Achondroplasia is the commonest, prototype nonlethal skeletal dysplasia accounting to a major proportion of patients with chondrodysplasias. It is the most frequent cause of short limb dwarfism. Chondrodysplasias are a group of skeletal dysplasia's which include lethal forms like than atophoric dysplasias (birth prevalence: 1 in 35,000 births), nonlethal forms like achondroplasias (birth prevalence of 1 in 15,000 to 1 in 40,000 births) and hypochondroplasias [8]. As a result of mutations, the receptors become activated, without physiologic ligands, which enhance negative regulation of bone growth.

In essence these mutations lead to gain of negative function. In mutations involving FGFR3, extent of receptor activation as well as site of mutation determines the severity of clinical phenotype [6,7]. These denovo mutations are associated with advanced paternal age (more than 36 years) during conception which was evident in the index case [4, 5]. It is also inherited as an autosomal dominant trait with complete penetrance [2]. Achondroplasia in both parents leads to 50% of affected heterozygous offspring's and 25% of homozygous affected offspring's, usually fatal form and the rest of 25% remain unaffected. On the other hand, if one parent is achondroplast, the chance of each child having this gene is 50% [11].

Impaired endochondral bone formation coupled with abnormal placement and premature fusion of the synchondrosis and unilateral oppositional periosteal bone growth leads to short and wide long bones**.** As the iliac crest oppositional growth remains normal, iliac wings are large and square shaped. Similarly, the abnormal growth of the triradiate cartilage (endochondral growth) leads to horizontal acetabular roofs. Therefore, these abnormal patterns of development are the basis for many of the phenotypic and radiological manifestations in achondroplasia.

The bones formed by endochondral ossification are affected sparing those formed by intramembranous ossification, thus the skull vault and spinal column is formed normally in achondroplasia. It affects almost all the bones of skeleton leading to bony changes alongside soft tissue changes all over the body. Abnormalities of endochondral ossification with premature synostosis of vertebral bodies and posterior arch result in thickened laminae, shortened pedicles and reduced height of vertebral bodies. These in turn lead to spinal stenosis and small foramen magnum, although the spinal column is not affected primarily.

Clinical features: Males are affected more than females as in the index infant. In the neonatal period, prominent features include short limbs, elongated narrow trunk, with a large head, prominent forehead and midfacial hypoplasia, depressed nasal bridge (saddle nose) which were evident in the present case. Birth length ranges from low to normal as in the index case. Limb length shortening is greater in the proximal segments (rhizomelic shortening) and 2^{nd}, 3^{rd} and 4^{th} digits are of equal length exhibiting a trident configuration [8, 9]. The index infant also had these characteristic phenotypic manifestations. Hyperextensibilty can be demonstrated in majority of the joints with elbow joint being an exception as duly noted in the present neonate. Other manifestations include narrow thoracic cage with protuberant abdomen, redundant skin folds on the limbs, which were also evident in the present case.

The manifestations in the later life most importantly include asymmetric short stature with an average adult height of about 131cms in males and 123cms in females followed by maxillary hypoplasia in relation with overcrowding of the teeth. Also, kyphosis or lordosis of the spinal cord with aberrations of CSF flow, delayed speech attainment, sleep apnoea and recurrent otitis media. Index neonate requires regular follow up to look for the evolution of these complications.

Diagnostic radiological features: Long bones are short and broad with metaphyseal flaring and typically long fibula compared to tibia as in this case. Metacarpals and phalanges of the hand are broad and short. The latter is more marked in proximal and middle phalanges as seen in the index case [8, 9].

Second, third and fourth digits show equal lengths with increased spacing between the third and fourth digits and thus confirming the trident hand configuration evident in this infant. With advancing age, coxa vara, bowing of tibia, short humerus with frequent radial head dislocation and inverted-V shaped pattern of distal femoral physes can be seen.

Frontal bossing with widened cranial vault are evident in this neonate. Small funnel shaped foramen magnum is also reported. Anteroposterior radiograph of lumbar spine shows gradual narrowing of interpedicular distance from L_1 to L_5 (narrowest at L_5), a characteristic manifestation [8, 9]. This was noted in the present case. Pedicular shortening and posterior scalloping of the vertebral bodies is seen in the lateral view. Midfacial hypoplasia, short and broad pelvis, square shaped ilium along with short sacrosciatic notch and horizontal acetabular roof are revealed in the pelvic x ray, was manifest in this infant. Unlike a normal neonate, which presents with a slanted inferior margin of the ilium, in an achondroplast neonate it is horizontal. The current infant also demonstrated this finding.

Achondroplasia in association with pulmonary hypoplasia leads to PPHN due to immature or abnormal growth of pulmonary vessels. However,in the current neonate PPHN was not associated with pulmonary hypoplasia. A varied degree of kyphosis of thoracolumbar spine is apparent in later life as the infant grows and need to be looked in follow up.

Prenatal diagnosis: Although fetal limb measurements in the second trimester can mark the presence of achondroplasia, the fetal changes are more prominent in the 3rd trimester making prenatal diagnosis less accurate prior to it. Prenatal sonographic features consist of Short FL ($<5^{th}$ centile) and reduced FL to BPD ratio**.** Usually, this FL/AC in achondroplast will be in between 0.16-0.19 which was seen in index case.

Management

Cesarean section should be preferred over normal vaginal delivery in a suspected case of achondroplasia in order to avoid CNS complications, which was implemented in this case. Achondroplastic stereotypical features are evident at the time of childbirth.

In the immediate neonatal period respiratory complications due to pulmonary hypoplasia require assisted ventilation. However, the presence of pulmonary hypoplasia carries a poor prognosis which was not there in the index case. Specific treatment for dwarfism in later age involves supplementation with growth hormone [12, 13]. Complications like stenosis of spinal canal will require surgical decompensation later on.

CONCLUSION

We report a term male neonate with achondroplasia and persistent pulmonary hypertension in the absence of pulmonary hypoplasia, characteristic clinical and radiological features confirmed by chromosomal analysis coupled with advanced paternal

age suggestive of denovo mutation makes this case unique.

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