Case Report

Jeune syndrome: Asphyxiating thoracic dystrophy and its genetic diagnosis – A rare case report

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ABSTRACT

Jeune syndrome, also known as asphyxiating thoracic dystrophy, is a rare multisystem potentially lethal skeletal dysplasia. It has an estimated incidence of 1/100,000–130,000 live births. A term outborn female neonate born by vaginal delivery to a primigravida mother, presented to our neonatal intensive care unit with severe respiratory distress since birth. The baby was noticed to have multiple characteristic skeletal anomalies including small bell-shaped thorax and short limbs leading to the clinical diagnosis of Jeune syndrome. Whole genome sequencing was done which confirmed the diagnosis. A correct clinical and genetic diagnosis in index cases of Jeune syndrome should be established to facilitate prenatal diagnosis and genetic counseling.

Key words: Asphyxiating thoracic dystrophy, DYNC2H1 gene, Genetic counseling, Jeune syndrome, Skeletal dysplasia

Asphyxiating thoracic dystrophy (ATD), also known as Jeune syndrome, was first described in 1955 by Jeune *et al*. in two siblings with severely narrow thorax [1]. It is a rare autosomal recessive disorder with variable severity and multiple musculoskeletal manifestations and a global incidence estimated of 1:100,000–130,000 live births [2]. Possibly because of the lack of reported data and paucity of structured perinatal database in our country, actual incidence is not available in the literature. The condition is characterized by short-limbed dwarfism, a small narrow bell-shaped thorax, micromelia, varying degrees of rhizomelic brachymelia, polydactyly of hands and feet, pelvic abnormalities, and renal anomalies with a considerable neonatal mortality up to 90% as a result of respiratory distress [3].

Severity of clinical and radiological features can vary possibly due to genetic heterogeneity. Mutations in four genes have been identified, namely, IFT80, DYNC2H1, TTC21B, and WDR19. Mutations in the TTC21B gene, encoding the retrograde intraflagellar transport protein IFT139, are associated with isolated nephronophthisis and ATD [4]. Restricted thoracic cage causing lung hypoplasia, can lead to alveolar hypoventilation and majority of patients of Jeune syndrome die from respiratory failure in infancy. In later infancy, they may present with renal, hepatic, ocular, and pancreatic complications. The prenatal diagnosis of fetal skeletal dysplasia is a challenging task as there could be large number of possible diagnosis. However, skeletal dysplasia in particular includes lethal diseases, which makes prenatal diagnosis in such cases highly important both medically and socially [5]. We describe a case that was diagnosed postnatally by clinical, radiographic and targeted genetic sequencing test-based analysis.

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CASE REPORT

A full-term outborn baby girl born to primigravida non-consanguineous married couple by normal vaginal delivery was referred to our hospital at 8 h of life. No significant antenatal risk factors were reported. Regular antenatal check-ups were done. Antenatal scan printed reports were not available. Mother reported normal fetal movements during pregnancy. Amniotic fluid index was normal. There was no history of fetal demise in the family members. There was no family history of skeletal anomalies. The baby required resuscitation at birth (details not known) and was noted to have respiratory distress. Birth weight was 4.1 kg with length and head circumference as 48 cm and 33 cm, respectively.

At admission, the baby was moderately active with severe respiratory distress. The Downe's respiratory score was 7/10, respiratory rate was 70/min with severe retractions, and SpO_2 was 70% in room air and 84% with oxygen. The baby had classical features of small narrow bell-shaped thorax, bilateral short upper limbs (rhizomelic shortening), and small hands with short metacarpals. The chest radiograph showed typical findings of

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horizontal short ribs, irregular enlarged costochondral junction with small, and horizontal clavicles (Figs. 1 and 2).

Due to impending respiratory failure, the baby was intubated and ventilated on high settings. The baby was put on synchronized intermittent mandatory ventilation mode of ventilation with a mean of 12 with FiO_2 of 100%. Oxygenation index (OI) was 18. In view of worsening clinical symptoms, OI was increased from 18 to 20, and the baby was put on a high-frequency oscillation ventilation with a mean of 15 and FiO_2 of 100%. Echocardiography done showed a structurally normal heart. USG abdomen showed normal kidneys and fundus examination was normal. By day 4 of life, the baby had significant hypoxemia with hypercarbia, developed progressive respiratory failure, and expired.

The diagnosis of Jeune syndrome was made based on clinical and radiological findings. Necessary blood samples of the baby for genetic testing by whole exome sequencing were sent. The parents too were offered the option of undergoing genetic testing which they refused due to financial constraints. The report at the end of 4 weeks showed compound heterozygous mutation of DYNC2H1 gene on chromosome 11 (Table 1).

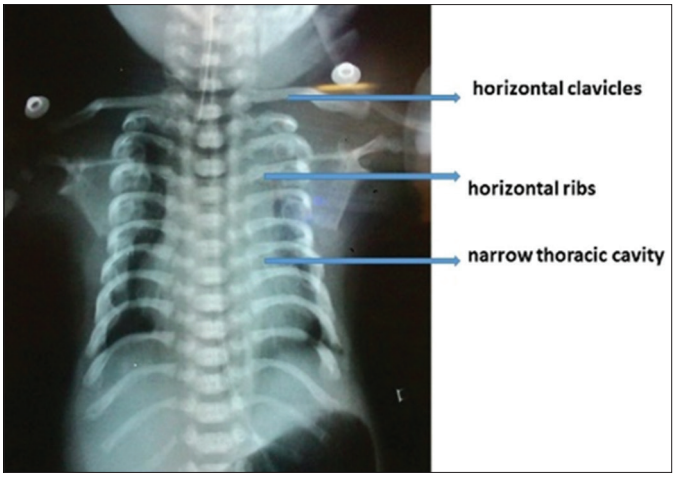

Figure 1: Chest radiograph

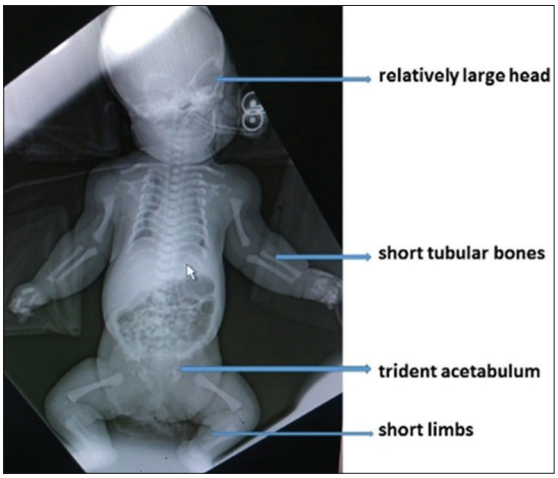

Figure 2: Infantogram

DISCUSSION

Jeune syndrome, also known as ATD, is known to be genetically heterogeneous and follows autosomal recessive pattern of inheritance. Short rib thoracic dysplasia classification is based on the molecular studies and gene involvement. The classic manifestations in infancy include dwarfism with short ribs, short limbs, polydactyly of hands and feet, characteristic radiographic changes in the ribs – small bell-shaped thorax, and pelvis – short iliac bones along with retinal degeneration [2].

The most common change in gene IFT80, DYNC2CH1 is found in 50% of cases [5]. The purpose of presenting the above case is to highlight the compound heterozygous genetic mutation of DYNC2H1 gene, which is a rarity. Schmidt *et al.* in their article described comprehensively the similar findings [6]. Baujat *et al*. reviewed 53 cases of ATD in 39 families both clinically and at molecular level and concluded DYNC2CH1 as the major gene responsible [7]. Badiner *et al*. reported three cases with gene sequencing and revealed compound heterozygosity for mutations in DYNC2H1 [8].

One of the most common antenatal features in these cases is oligoamnios, indicating associated renal anomalies. In the present case, we could not get the printed copy of the antenatal scan, thus raising doubts on the quality and reliability of the ultrasound scans if actually done. The diagnosis of spectrum of skeletal dysplasias is mainly based on measurements such as femur length (FL), thoracic circumference (TC), rib cage diameter, abdominal circumference (AC), and TC/AC ratio. Based on these measurements, we can diagnose abnormalities such as mesomelic (shortening of radius and ulna in upper limb and tibia and fibula in lower limb), rhizomelic (shortening of humerus in upper limb and femur in lower limb), and micromelic (shortening of all tubular bones), chest circumference <5th percentile for gestational age suggests lung hypoplasia, and FL/AC ratio <0.16 suggests lung hypoplasia. Other ultrasonographic findings include polyhydramnios and absent or feeble respiratory movements [2].

Lung hypoplasia, presumably due to restricted thoracic cage, causes alveolar hypoventilation and approximately 60–70% of patients of Jeune syndrome die from respiratory failure in infancy. Other skeletal dysplasias which are close mimics are achondrogenesis, achondroplasia, osteogenesis imperfecta, thanatophoric dwarfism, and hypophosphatasia [9]. The diagnosis is based on radiologic findings and genetic diagnosis. Management is mainly supportive including ventilation. The severity depends on the extent of restrictive lung disease and other associated multisystem involvement. Surgical option of

Table 1: Gene: Location exon 49 and 54 disease name (OMIM): Short-rib thoracic dysplasia-3 with or without polydactyly

Gene	Location	Variant	Zygosity	Amino acid substitution
DYNC2H1 (+) on chromosome 11	Exon 49	c.7894G>G/A, p.Glu2632Lys	Heterozygous	Lysine for glutamic acid at codon 2632
	Exon 54	c.8580A>A/T, p.Glu2860Asp	Heterozygous	Aspartic acid for glutamic acid at codon 2860

bilateral thoracic expansion has been reported to have benefit in few cases [10].

CONCLUSION

Jeune syndrome should be considered as a differential diagnosis in a neonate with skeletal dysplasia and respiratory distress. Prenatal diagnosis is possible with a detailed antenatal scan and fetal biometry. Postnatal diagnosis is based on radiologic findings and genetic diagnosis. Management is mainly supportive including ventilation. It is a rare lethal skeletal dysplasia for which a correct genetic diagnosis can help in counseling.

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