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Case Report

A rare case of spondyloepimetaphyseal dysplasia with joint laxity, type 3 (EXOC6B gene) (SEMDJL3)

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ABSTRACT

Spondyloepimetaphyseal dysplasia with joint laxity, type 3 (SEMDJL3) is an ultra-rare condition, inherited in autosomal recessive manner caused by mutations in EXOC6B gene, encoding a component of the exocyst complex, crucial for cell growth and exocytosis. It is characterized by multiple joint dislocations, joint laxity, genu valgum, short stature, and skeletal dysplasia. There are approximately 6 confirmed cases reported worldwide and only one or two cases in India. Patient presented with complain of not gaining height and was later diagnosed with SEMDJL3.This case review aims to increase awareness of this rare disorder, which remains underdiagnosed due to the scarcity of documented cases and some overlap with other syndromes.

Keywords: Spondyloepimetaphyseal dysplasia with joint laxity type 3, Ultra rare, EXOC6B gene

INTRODUCTION

Spondyloepimetaphyseal dysplasia with joint laxity, type 3 is an ultra-rare condition, caused by homozygous mutation in the EXOC6B gene.[1,2] It is characterized by multiple joint dislocations at birth, severe joint laxity, scoliosis, genu valgum, short stature, delayed bone age.[3,4]

The first cases of SEMD with joint laxity were described decades ago, but only in the last 10 years has the EXOC6B-related subtype been genetically defined.[2] To date, fewer than 10 individuals worldwide have been reported, highlighting its extreme rarity and the importance of genetic testing for diagnosis.

CASE REPORT

A case of 20-month-old girl child of Indian ethnicity, born of non-consanguineous marriage was presented with complain of not gaining height. She was born at term via normal vaginal delivery, with a birth weight of 2.4 kg. Birth length was not noted. She did not require neonatal intensive care unit admission. There were no other hospital admissions, but complain of recurrent cough and cold, for which she requires nebulization.

Her mother was HBsAg positive during her birth. There is history of previous 3 sibling death. Two female sibling death within 24 hours of birth due to prematurity (Figure 1).

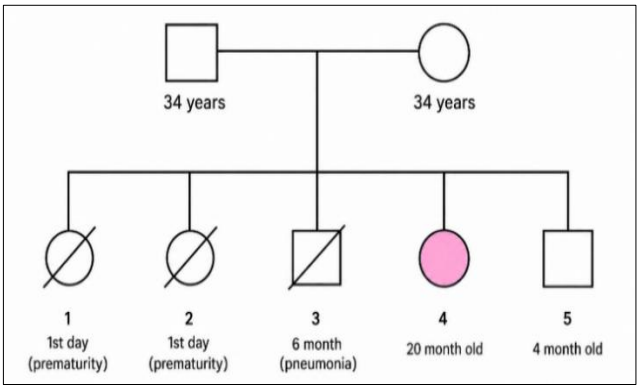

Figure 1: Pedigree chart of family.

Her antenatal scan had shown early epiphyseal closure. Her development milestones are age-appropriate except for a delay in motor skills (standing with support, immature pincer grasp). Standing with support is been shown in Figure 2.

Figure 2: Short stature, standing with support.

She has kyphoscoliosis (Figure 3) and genu valgum. No wrist widening was noted. No carpal bones were noted in her X-ray (Figure 4).

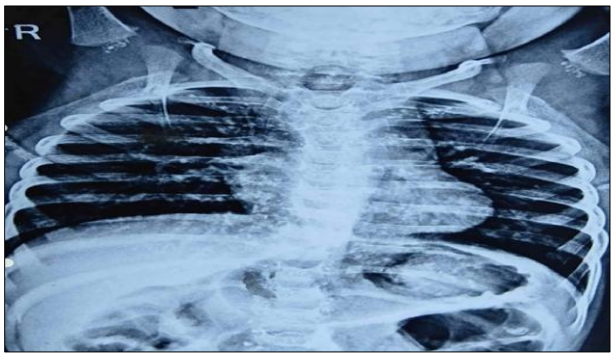

Figure 3: Thoracic spinal deformity with scoliosis.

She is suspected to be affected with chondrodysplasia (higher upper/lower segment ratio), so we directly evaluated her for pathogenic variations (as antenatal scan showed early epiphyseal closure) and went for whole exome sequencing.

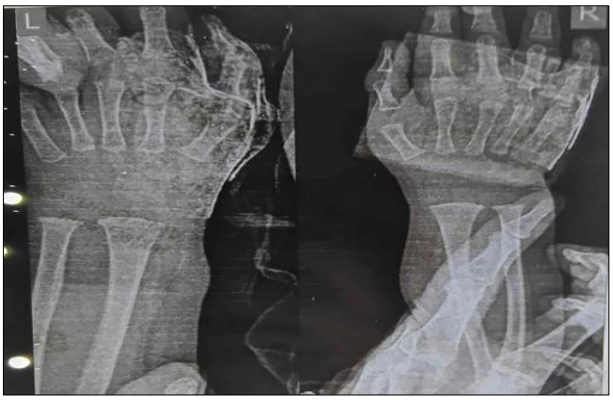

Figure 4: No carpal bone.

Table 1 shows anthropometry data at 20 months. Table 2 shows blood investigations.

Table 1: Anthropometry.

Variables	Values
Height	70 cm (<-3 SDs)
Weight	7.9 kg (<-3 SDs)
Head circumference	43 cm
Chest circumference	52 cm
Upper segment: lower segment	1.3:1 (slightly elevated)
Weight/age	<-2 SDs
Height/age	<-3 SDs

Diagnosis

The diagnosis of EXOC6B-SEMD-JL is established by biallelic pathogenic variants in *EXOC6B* identified by molecular genetic testing (whole exome sequencing) (Table 3).

Table 2: Blood investigation.

Investigation profile	Variables
Haemoglobin (11.5-17 g/dl)	10.6
WBC (4000-11000 cells/cumm)	6600
Platelets (150000-500000 cells/cumm)	381000
S. Calcium (8.5-10.5 mg/dl)	9.9
S. Urea (20-40 mg/dl)	24
S. Creatinine (0.7-1.4 mg/dl)	0.8
ALT (0-34 U/l)	19
ALP (40-130 U/l)	131
Peripheral smear	Normocytic normochromic blood picture with anisocytosis, microcytes+
HBsAg, HCV antibody, HIV	Negative
Thyroid profile	TSH-0.8 µIU/ml (0.35-4.94 µIU/ml), T3-0.9 ng/dl (0.35-1.93 ng/dl), T4-8.2 µg/dl (4.87-11.72 µg/dl)
2D ECHO	Normal

Continued.

Investigation profile	Variables
TORCH profile	CMV IgG 51.9 AU/ml (reactive >12.0)
Ophthalmological examination	Normal
X-ray	CXR-punctate calcification seen at bilateral humeral head, along scapular border and at transverse processes of visualised vertebrae on both sides, p/o chondrodysplasia punctate, X-ray wrist-no carpal bone
Whole exome sequencing	Mentioned below

Table 3: The diagnosis of EXOC6B-SEMD-JL.

Gene (transcript)#	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
EXOC6B (-) [ENST00000272427. 11]	chr2:g.(72575669_72718102)_(72741470_72825797)del	c.(113+1_114-1)_(669+1_670-1) [Exonic deletion]	Homozygous	Spondyloepimetaph-yseal dysplasia with joint laxity, type 3 (OMIM#618395)	Autosomal recessive	Likely pathogenic

DISCUSSION

Spondyloepimetaphyseal dysplasia (SEMD) constitute a heterogeneous group of skeletal disorders characterized by abnormalities in the spine, epiphyses, and metaphysis.[5]

SEMDJL3 is a distinct subtype, an ultra-rare condition, which is caused by homozygous mutation in the EXOC6B gene.[2,4] Because it was only recently linked to the EXOC6B gene (with major studies emerging around 2022-2024), the number of officially documented cases is extremely low.

The total number of patients is likely higher but currently undiagnosed at the molecular level. Till date, there are approximately 6 to 10 confirmed cases reported worldwide in clinical literature.

The first reported medical cases of SEMDJL3 were published in 2016 which described two Indian siblings with congenital joint dislocations, severe joint laxity, short stature, spinal abnormalities, and characteristic skeletal X-ray findings.[2] No newer cases beyond 2022 have been published in indexed literature.[1] It is characterized by multiple joint dislocations at birth (hips and knees), severe joint laxity, scoliosis, genu valgum, short stature, gracile metacarpals and metatarsals, delayed bone age, and poorly ossified carpal and tarsal bones. Dislocations can also occur at the elbows, wrists, ankles, and patellae.[3]

EXOC6B encodes a component of the exocyst complex required for tethering secretory vesicles to the plasma membrane and primary ciliogenesis.[1] It is a multimeric protein complex necessary for exocytosis, which in turn, is crucial for cell growth, polarity and migration. Mutations disrupt skeletal development, leading to abnormal ossification and connective tissue weakness which explains the joint laxity and dislocations.

SEMDJL3 is frequently misdiagnosed as SEMDJL1 (Beighton type, B3GALT6 mutations) due to overlapping features of joint laxity and spinal deformity. However, SEMDJL3 often presents with more pronounced congenital dislocations and specific radiographic markers. It must also be differentiated from SEMD-JL (hall type or leptodactylic type), KIF22 mutation, spondylodysplastic type 1 (B4GALT7 mutation) and Ehlers-Danlos syndrome.

Management is focused on improving quality of life, as there is currently no cure for the underlying genetic mutation. This includes-Early orthopedic intervention to reduce and stabilize hip and knee dislocations to allow for mobility and as and when needed for scoliosis and kyphosis. Physical therapy to maintain joint mobility and muscle strength and regular monitoring of the spine for curvature: the spine must be checked regularly for curvature, watch for neurological issues (like spinal cord compression).

Diagnosis usually begins with a physical exam and is confirmed through skeletal surveys (joint dislocations, flattened vertebrae, progressive scoliosis or kyphosis, slender tubular bones, metacarpals, phalanges and ribs, metaphyseal striations and irregularities, epiphyseal flattening and delayed ossification, delayed ossification of carpal and tarsal bones, shallow acetabula, irregular femoral heads) and genetic testing.[1-5]

Counselling

Families can receive accurate recurrence risk estimates (25% for siblings) as it has autosomal recessive inheritance. Parents must be screened for the mutation in the affected gene.

Our case of SEMD with joint laxity, type 3 (SEMDJL3), shares a genetic basis with referenced cases, involving mutations in the EXOC6B gene. Clinically, common features include short stature, higher upper/lower segment ratio, skeletal dysplasia, kyphoscoliosis and delayed motor milestones. Genetic analysis confirmed the diagnosis in

our case, underscoring its importance in diagnosing rare genetic disorders accurately. Unique to our case is its geographical rarity, being the first reported instance in Gujarat, India. Clinical uniqueness includes no history of congenital joints dislocation which highlight variability in manifestations. These differences emphasize the need for increased awareness and further research to enhance diagnostic capabilities and understanding of this complex genetic syndrome.

CONCLUSION

A case of 20-month-old female patient presented with disproportionate short stature was presented. Genetic analysis showing homozygous mutation in EXOC6B gene suggestive of SEMD with joint laxity, type 3 (SEMDJL3). This is the first reported case in Gujarat and one of the rare cases in India. This report adds to the limited global database of SEMDJL3. The rarity of SEMD with joint laxity, type 3 (SEMDJL3) highlights the need for increased awareness and importance of considering genetic disorders when common conditions are ruled out.

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