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Case Study on Rare Disease: Liberfarb Syndrome

Dr. Pankti Shah[1], Dr. Ankur Patel[2], Dr. Khushbu Chaudhari[3], Dr. Kirti Mehta[4]

[1]2nd Year Resident, Department of Pediatrics, Government Medical College, Surat
Corresponding Author Email: *shahpankti1403[at]gmail.com*

[2, 3]Assistant Professor, Department of Pediatrics, Government Medical College, Surat

[4]Associate Professor, Department of Pediatrics, Government Medical College, Surat

Abstract: ***Liberfarb Syndrome is a type of Spondyloepimetaphyseal Dysplasia involving connective tissue, bone, retina, ear, and brain. Patients exhibit severe short stature and scoliosis with thoracic kyphosis and lumbar hyper lordosis. Severe joint laxity results in dislocation of elbows, hips, and knees. Eye findings are consistent with early - onset retinal degeneration, and there is moderate to severe early - onset hearing loss. Microcephaly is apparent by school age, and patients exhibit developmental delay and intellectual deficit[1]. Clinical variability has been observed, with some patients presenting differences in the severity and location of skeletal dysplasia involvement as well as variation in other features of the syndrome[2].***

Keywords: Liberfarb Syndrome, Spondyloepimetaphyseal dysplasia, short stature, Microcephaly

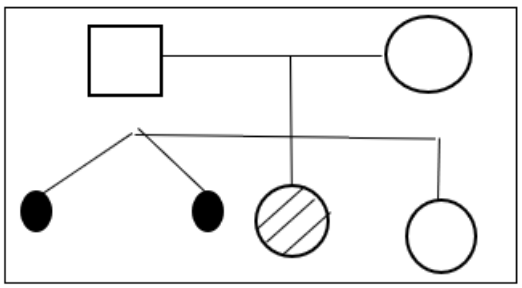
1. Introduction

Spondyloepimetaphyseal Dysplasia (SEMD) are a group of genetically heterogeneous skeletal disorders characterized by abnormal vertebral bodies and epimetaphyseal abnormalities[3]. Liberfarb Syndrome is a multisystem Disorder affecting bone, eye, ear and brain development caused by founder pathogenic variant in the PISD Gene (phosphatidylserine decarboxylase). It is Autosomal Recessive Disorder associated with severe short stature, failure to thrive, scoliosis, intellectual delay, early onset retinal degeneration and sensorineural hearing loss.

2. Case Report

Two Year Female child born out of non - consanguineous marriage presented to Pediatric OPD with complaint of not gaining adequate height and weight.

- BIRTH HISTORY: Full - term, AGA (Appropriate for gestational age), Normal vaginal delivery, Birth weight 1.7Kg and uneventful birth events.
- FAMILY HISTORY: No history of short stature in the family.
- IMMUNIZATION HISTORY: Patient's immunization was appropriate for age as per National Immunization Schedule.
- PEDIGREE ANALYSIS: suggests still born twin delivery and younger sister (4 - month age) – normal stature.



- DEVELOPMENTAL HISTORY: Developmental Milestones achieved appropriately for age.
  a) Gross Motor: Patient was able to sit without support at 1 year of age. Patient was able to stand alone and walk with support at 2 years of age.
  b) Fine Motor: Patient was able to scribble.
  c) Language: Patient could speak 1–2 - word sentence.
  d) Social: Patient played with siblings, asks for food.

- GROWTH:
  a) Height: 61 cm (height for age < 3 rd. Centile)
  b) Weight: 6 kg (weight for age < 3 rd. Centile)
  c) Head Circumference: 45 cm (Head Circumference for age < - 1 SD)
  d) Maternal Height: 155 cm
  e) Paternal Height: 165 cm

a) On General Examination:
Patient was alert, active and playful.
Head to Toe examination suggestive of:

- Anterior fontanelle wide open with microcephaly Depressed Nasal Bridge
- Scoliosis
- Short long Bones (Rhizomelic Short Stature)
- Brachydactyly

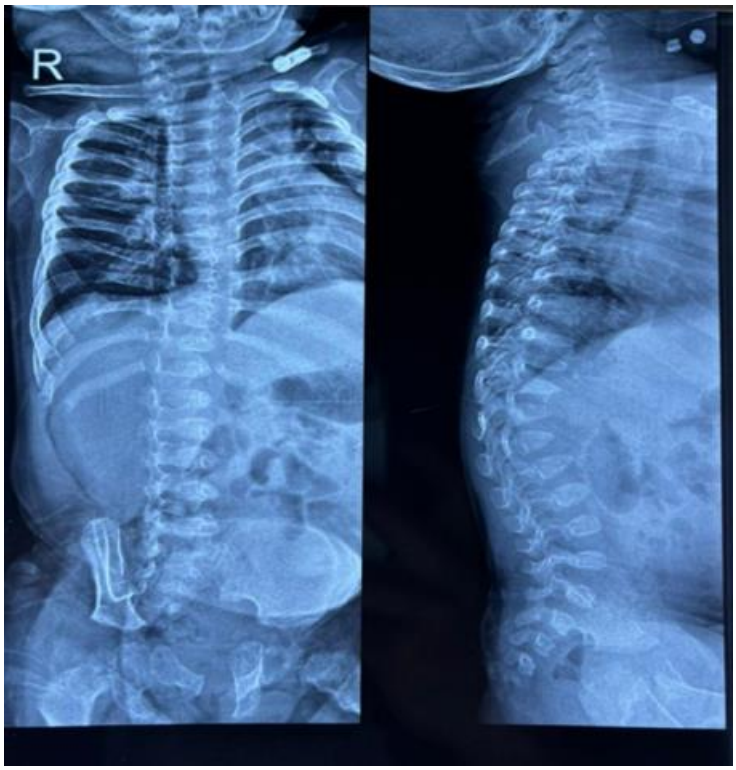
No pallor, icterus, cyanosis, clubbing, koilonychia or lymphadenopathy was seen.

b) Systemic Examination

- Cardiovascular System: S1, S2 present, No murmur
- Respiratory System: AEBE Clear
- Per Abdomen: soft, non - tender
- Central Nervous System: NAD

c) Investigations:

- Ophthalmic Examination: Normal visual Acuity with normal fundus examination
- ENT Examination: Normal Hearing (No SNHL)
- Xray Spine (PA view and Lateral view): Scoliosis



2 D Echo was normal.

- USG Abdomen was normal.
- Whole exome sequencing for this patient was done suggestive of Liberfarb Syndrome (OMIM618889)
- GENE: PISD (ENST00000439502.6)
- LOCATION: Exon 7
- VARIANT: c.899G>A (p. Cys300Tyr)
- ZYGOSITY: Homozygous
- INHERITANCE: Autosomal Recessive
- CLASSIFICATION: Likely Pathogenic

3. Discussion

Liberfarb et al. (1986) [4] described an 11 - year - old girl with severe pigmentary degeneration of the retina associated with severe musculoskeletal abnormalities, growth failure, recurrent respiratory problems, sensorineural hearing loss, and mental retardation. The musculoskeletal abnormalities included short, long bones, hyper extensible joints, scoliosis, lordosis, spina bifida occulta, dislocated radial heads, dislocated hips, and valgus deformities of the knees with laterally dislocated patellae.

Liberfarb Syndrome (LIBF) is caused by homozygous mutation in the PISD gene (612770) on chromosome 22q12 [7]. The enzyme phosphatidylserine decarboxylase (PISD) is responsible for the conversion of phosphatidylserine (PS) to phosphatidylethanolamine (PE), a process that is essential in all living organisms[5]. PE is an abundant phospholipid in cellular membranes and is particularly enriched in mitochondrial membranes. PISD is located in the inner mitochondrial membrane of eukaryotic cells [6] and it was shown to be essential for the production of PE in situ.5 The available evidence suggests that recessive PISD variants may be responsible for quite divergent clinical phenotypes, possibly related to the severity of the variants detected, ranging from apparently isolated skeletal dysplasia to multisystemic conditions affecting brain, ear, eye, connective tissue, and bone. The pathogenesis remains unclear, but the accumulating evidence, including other rare families segregating pathogenic variants in PISD, points to a pleiotropic and variable phenotypic spectrum possibly related to mitochondrial dysfunction ("mitochondrial chaperonopathies") and to phospholipid synthesis disorders.6

Other than skeletal Abnormalities, retinal degeneration is the second cardinal feature. The fundus findings were pale optic disks, RPE mottling, severely reduced caliber of the retinal vessels, and areas of bone spicule pigment deposition. These findings are compatible with EORD.6

4. Conclusion

Liberfarb Syndrome (LIBF) caused by homozygous mutation in the PISD gene (612770) on chromosome 22q12 severe pigmentary degeneration of the retina associated with

severe musculoskeletal abnormalities, growth failure, recurrent respiratory problems, sensorineural hearing loss, and mental retardation. Clinical variability has been observed, with some patients presenting differences in the severity and location of skeletal dysplasia involvement as well as variation in other features of the syndrome.

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