

Split Hand Feet Malformation in a Term Newborn with Involvement of All Limbs: A Case Study

Zenab Yusuf Tambawala^a, Manal Wahba^a, Haneena Haneefa^a, Maram Hassan^b

^aDepartment of Obstetrics and Gynecology/Dubai Hospital /Dubai/UAE

^bMedical Education Department/ Alexandria Faculty of Medicine

Corresponding Author: Maram Hassan,

E-mail: maramhassan12@hotmail.com, 0020-122-8184354, Orchid ID 0000-0001-7477-5608

ABSTRACT

Background: A primigravida in the mid-20s presented with an anomaly scan showing limb deformity in all four limbs with fused fingers and ventricular septal defect. The patient did not have any other co-morbidities or any drug exposure during her pregnancy. Ectrodactyly refers to a congenital limb malformation characterized by the absence of one or more central digits, resulting in a cleft or "lobster claw" appearance.

Objective: Whether isolated or part of a genetic syndrome, the management of this condition often involves a multidisciplinary team to manage and provide appropriate care including genetic counseling, orthopedic specialists, and other relevant healthcare professionals.

Patient and methods: A primigravida in the mid-20s presented with an anomaly scan showing limb deformity in all four limbs with fused fingers and ventricular septal defect.

Results: The delivery of a baby with SHFM is generally managed like that of any other newborn. However, postnatal care and follow-up involve a collaborative effort between a multidisciplinary team to ensure comprehensive care for the baby and support for the family.

Conclusion: Surgical interventions may be considered to address limb anomalies and enhance functionality. Early intervention and support can help improve the individual's quality of life and functionality.

Keywords: Split hand feet malformation, Genotype, Phenotype.

INTRODUCTION

Split Hand Feet Malformation (SHFM), previously known as ectrodactyly, is a rare condition, with 1 in 8,500-25,000 newborns presenting, and can be sporadic, genetic, or non-genetic syndrome⁽¹⁾.

Second-trimester ultrasound can easily identify the condition. Many previously published reports showed women terminating their pregnancy at identification of ectrodactyly, although it is usually non-lethal with normal fetal karyotype and most babies do not have other co-morbidities or development defects⁽²⁾.

SHFM can present with significant clinical variability, irregular inheritance patterns, and a wide range of molecular genetic alterations, which collectively make accurate diagnosis and prognosis assessment challenging. SHFM can manifest in various ways, ranging from mild to severe forms. In some cases, only a few digits may be affected, while in others, entire hands or feet may be split. This variability in the clinical presentation can complicate diagnosis, especially when the condition is mild or when it presents with atypical features⁽¹⁾.

SHFM does not follow a simple Mendelian inheritance pattern in many cases. It can be inherited in an autosomal dominant, autosomal recessive, or even X-linked manner, depending on the specific genetic mutations involved. Additionally, some cases may occur sporadically without a family history, making it

challenging to predict the risk of recurrence in future generations⁽³⁾.

Single gene mutation, chromosomal rearrangement, balanced translocations, or inversions can be associated with this condition and although most cases are sporadic, diagnosis and assessment of the risk of recurrence and management are challenging⁽¹⁾.

PATIENT AND METHODS

A primigravida in her mid-20s who was in a non-consanguineous marriage for a year sought medical care from early pregnancy. At 12 weeks of gestation, she underwent a routine nuchal translucency scan, which was normal. The anomaly scan by the radiologist at 20 weeks was suggestive of abnormalities in the hands and feet. She was referred to the Fetal-Maternal Medicine Unit at our Tertiary Care Center for additional follow-up and counseling.

The patient had a cousin with limb deformity with fused fingers. During the fetal medicine ultrasound scan at 22 weeks, a single active fetus in a variable position with the presence of an anterior placenta was noted. Fetal parameters were consistent with the gestational age, and the amniotic fluid volume was found to be within the normal range. The hands and feet displayed missing fingers and toes (the left hand had missing second and third fingers, the right hand had only two fingers, and both

feet had missing middle toes). The fetal anatomy was found to be normal. The basic heart examination showed a normal four-chamber view, normal three-vessel view, and normal left ventricular outflow tract (LVOT) and right ventricular outflow tract (RVOT), with a small perimembranous and muscular ventricular septal defect (VSD).

At 25 weeks, a fetal echocardiogram (ECHO) was performed, which confirmed the presence of a moderate mid-muscular VSD measuring 4 mm. The parents were provided with detailed genetic counseling regarding the potential screening options available for identifying genetic disorders, including the utilization of cell-free DNA testing by non-invasive prenatal testing (NIPT) and the subsequent confirmation of diagnosis through amniocentesis. However, they instead opted for postnatal whole-exome genome sequencing for the newborn and comprehensive genetic information after birth.

She had regular weekly follow up at the Fetal Medicine Management Unit (FMMU) team for fetal growth and well-being assessment. At 40 weeks and 2 days, the patient had spontaneous onset of labor and was delivered by vacuum-assisted vaginal delivery under epidural analgesia.

The neonate born with normal APGAR scores and thorough evaluation by a neonatologist immediately after birth showed missing digits affecting both fingers and toes with bilateral cleft foot with syndactyly (fusion of adjacent digits) and a right hand with four fingers without a cleft, while the left hand displayed a cleft. Pediatric orthopedic consultation revealed that the baby had only two digits on the right hand and the left hand had a lobster hand deformity, which is characterized by the splitting or clefting of the hand. Additionally, the baby exhibited a split feet deformity affecting both feet. However, the

examination of the knees, hip, and spine showed no abnormalities.

A skeletal survey of the hands and feet to further assess the extent of skeletal involvement was advised to obtain a comprehensive view of the bones in the affected areas. The parents were also instructed to schedule follow-up visits at the clinic for continued monitoring and management of the baby's condition. After the evaluation by the pediatric genetic and metabolic specialist, a genetic panel was conducted (Figure 1).

Statement of Ethics

All data were collected and photographed after a signed informed consent was obtained from the parents of the newborn. The case study was approved by the ethics committee at Dubai Hospital.

Investigation and results

BERA (Brainstem Evoked Response Audiometry test) showed normal hearing in both ears and newborn screening for genetic, hormonal, and metabolic conditions was normal.

The skeletal survey was performed when the baby was 12 days old, which showed normal X-ray of the spine, non-displaced fracture of the right clavicle, absence of the 3rd, 4th, and 5th rays, including metacarpals of the right upper extremity, splaying of metacarpals and absence of the middle finger of the left upper extremity. The forearm and humerus were normal. There was an absence of the 3rd ray, with a fusion of the 4th and 5th metatarsals in the right lower limb.

The left lower limb had short 3rd and 4th metatarsals with absent toes with soft tissue syndactyly (fusion) of the 1st and 2nd toes (Figure 1.)


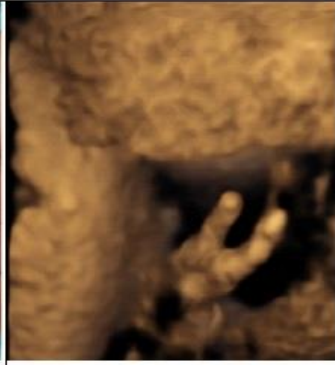


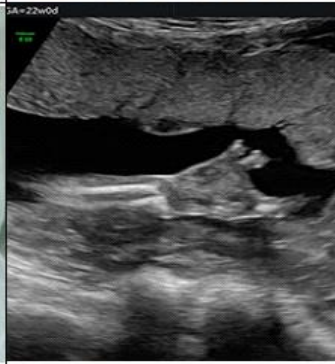





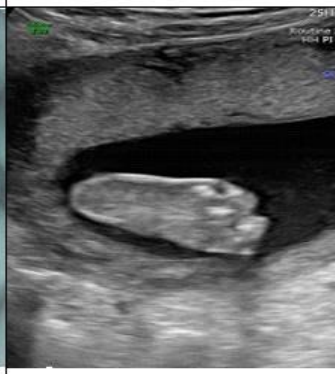

| | | | |
|---|---|--|---|
| <p>Right Upper limb</p> <p><i>Absence of the 3rd, 4th, and 5th rays, including metacarpals.</i></p> |  |  |  |
| <p>Left Upper limb</p> <p><i>Splaying of metacarpals and absence of the middle finger.</i></p> |  |  |  |
| <p>Right Lower limb</p> <p><i>Absence of the 3rd ray with fusion of the 4th and 5th metatarsals</i></p> |  |  |  |
| <p>Left Lower limb</p> <p><i>Short 3rd and 4th metatarsals with absent toes. Soft tissue syndactyly (fusion) of the 1st and 2nd toes</i></p> |  |  |  |

Figure (1): Examination, ultrasound, and X-ray of every limb.

The infant Hips' sonography showed no evidence of developmental dysplasia of the Hip (DDH). Ultrasound of the abdomen was unremarkable. Neonatal Echocardiography showed normal intra-cardiac anatomy, function, and size. Post-delivery neonatal EXOME analysis for 55 genes associated with the condition identified a hemizygous variant of uncertain significance in the NSDHL gene. Split Hand Foot Malformation Panel detected a hemizygous variant c.902A>G p.(Tyr301Cys) of unknown significance in the NSDHL gene, implying that it was unlikely to be the cause of anomalies in this infant. To further analyze if this variant was de novo or inherited, Total Variant Analysis (TVA) of the mother was requested and to check possible chromosomal rearrangements as a possible cause of microarray was done, results were awaited.

DISCUSSION

The NAD(P) dependent steroid dehydrogenase-like (NSDHL) gene found in the neonate is associated with NSDHL-related disorders, notably CHILD syndrome and CK syndrome^(4, 5).

CHILD syndrome, an X-linked disorder primarily affecting females, is often lethal for males during gestation. It manifests with ichthyosiform nevus and limb defects, which are not present in this case⁽⁴⁾. CK syndrome, another X-linked disorder primarily affecting males, is characterized by cognitive impairment, behavioral problems, early-onset seizures, cerebral cortical malformations, microcephaly, distinct facial features, a slender habitus, elongated digits, and occasionally, scoliosis, kyphosis, strabismus, and optic atrophy. The baby did not exhibit these phenotypic features⁽⁵⁾.

Given the absence of consistent clinical characteristics associated with these disorders, it is probable that the hemizygous NSDHL gene variant is not the primary causative factor for the condition. Further investigations have been initiated to clarify the origin of this variant, including Transmission Variant Analysis (TVA) for the mother and a microarray analysis to explore potential chromosomal rearrangements^(4, 5).

There are many genotypic and phenotypic variations of SHFM⁽¹⁾. Syndromal and Non-syndromal forms of SHFM are noted with highly variable clinical presentations, in the members of the same family and limbs of the single affected individual as well. It has also been classified as typical (multiple family members affected, symmetric limb involvement, and atypical (unilateral absence of central digital rays, usually non-heritable)⁽⁴⁾.

SHFM can also be classified based on genetic derangements, such as single gene mutation (SHFM type 1; SHFM type 4; SHFM type 6), recurrent genomic duplication (SHFM type 3), balanced/unbalanced translocations (SHFM type 5), and established loci identified by linkage analysis (SHFM type 2). Many other phenotypic abnormalities like congenital deafness, developmental dysplasia of the hip, absent fibula, cardiac anomalies, and skin manifestations may be associated with SHFM.^(1, 3, 6)

In summary, SHFM has a complex and highly variable genetic and phenotypic presentation. Providing management and accurate risk assessment for future pregnancies is difficult and multispecialty input and genetic counselling is essential.

○ Follow-up

This infant is being managed by a multidisciplinary team consisting of orthopedics, specialist hand surgeons, physiotherapists, genetic counselors, and pediatricians.

○ Learning points/take-home messages.

- Early antenatal diagnosis of Split hand feet malformation/ectrodactyly can help prepare for neonatal care.
- Important to rule out other associated ectodermal, auditory, cardiac, and bone abnormalities.
- Multidisciplinary long-term management with an obstetrician, pediatrician, geneticist, orthopedist, and physiotherapist is needed.

○ **Acknowledgment:** To all doctors involved in clinical care including radiologists, fetal medicine specialists, neonatologists, orthopedics, genetic counselors, and physiotherapists.

○ **Conflict of Interest Statement:** No conflicts of interest to declare.

○ **Funding Sources:** The study did not receive any funding sources.

REFERENCES

1. **Gurrieri F, Everman D (2013):** Clinical, genetic, and molecular aspects of split-hand/foot malformation: An update. *Am. J. Med. Genet. A.*, 161: 2860–72.
2. **Leung K, MacLachlan N, Sepulveda W (1995):** Prenatal diagnosis of ectrodactyly: the ‘lobster claw’ anomaly. *Ultrasound Obstet. Gynecol.*, 6: 443–6.
3. **Restelli M, Lopardo T, Lo Iacono N, Garaffo G, Conte D, Rustighi A et al. (2014):** DLX5, FGF8 and the Pin1 isomerase control $\Delta Np63\alpha$ protein stability during limb development: a regulatory loop at the basis of the SHFM and EEC congenital malformations. *Hum. Mol. Genet.*, 23: 3830–42.
4. **Hettiarachchi D, Panchal H, Lai P, Dissanayake V (2020):** Novel variant in NSDHL gene associated with CHILD syndrome and syndactyly- a case report. *BMC. Med. Genet.*, 21: 164.
5. **Preiksaitiene E, Caro A, Benušienė E, Oltra S, Orellana C, Morkūnienė A et al. (2015):** A novel missense mutation in the NSDHL gene identified in a Lithuanian family by targeted next-generation sequencing causes CK syndrome. *Am. J. Med. Genet. A.*, 167: 1342–8.
6. **Jaiswal S, Soni S, Patel C, Suthar A (2015):** Split hand/split-foot malformations: a report of four cases in a family with variable presentations. *Int. J. Res. Med. Sci.*, 28: 67–9.