Case Report

An Unusual Presentation of Bilateral Split Hand-Foot Malformation (SHFM) in Family: A Tale of Two Generations

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ABSTRACT: Split-hand/foot malformation (SHFM), also called as ectrodactyly. SHFM is a natural limb deformity, characterized by a deep standard split of the hand and/ or foot due to the absence of the central shafts. SHFM may happen as a separate existent or as part of a syndrome. Both forms are constantly established in association with chromosomal rearrangements resemblant to translocations or deletion. It is clinically and genetically diverse and shows substantially autosomal dominant heritage with variable expressivity and reduced penetrance. Cases presenting with SHFM features should be rigorously diagnosed, clinically examined, and submitted to pertinent cytogenetic and/ or molecular testing. We presented two months old male child and his paternal grandmother with SHFM.

KEYWORDS: *Split hand and foot malformation, autosomal dominant, congenital malformation, limb deformity, genetic counselling, ectrodactyly.*

Introduction

Ectrodactyly also known as Split-hand/foot malformation (SHFM) is a congenital limb developmental malformation, characterized by a variable degree of deep median clefts of the hands and/or feet due to the absence of central rays of extremities [1].

SHFM is inherited as an autosomal dominant, recessive, or X-linked entity, with a prevalence of 1 in 90,000 live births, and its clinical severity varies from patient to patient as well as between the limbs of the same patient [2].

Twelve different types of SHFM have been mapped to different human chromosomes.

We report a rare sporadic case of isolated SHFM with a tale of two-generation most likely caused by de novo mutation and discuss its etiology, pathogenesis, classification, genetic counseling, and management.

Case Presentation

A two-month-old male child was brought with a history of malformed hands and feet since birth. It was a teenage pregnancy. The child was delivered by Caesarean section.

The affected child was first in birth order, born out of a non-consanguineous marriage.

There was no history of drug intake or exposure to radiation during the antenatal period.

The mother never developed any febrile illness in the pregnancy nor was admitted for any other illness in the pregnancy period or earlier.

On examination bilateral feet have a midline cleft with aplasia of the second toe, and fusion of third and fourth toes.

The bilateral hand has a midline cleft with syndactyly of third and fourth fingers with extra finger beside thumb on right hand and aplasia of the third finger on the left hand.

On X-ray radiographs, all the metacarpals and metatarsals are normally developed with aplasia, syndactyly, and polydactyly seen in the toes and fingers (Figure 1,2).

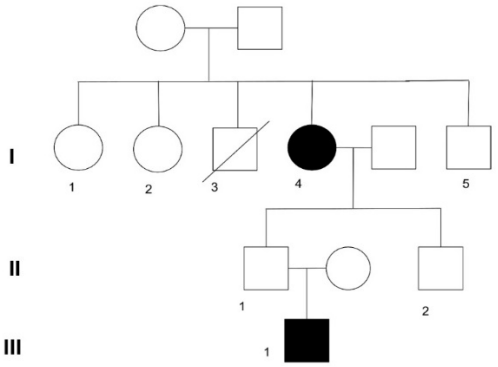

Figure 1. Pedigree chart of generation of the family with SHFM. The square box represents Male and Circle represents Female. The shaded square and circle represent patients. The number represents the members of the family of generations I, II, and III.

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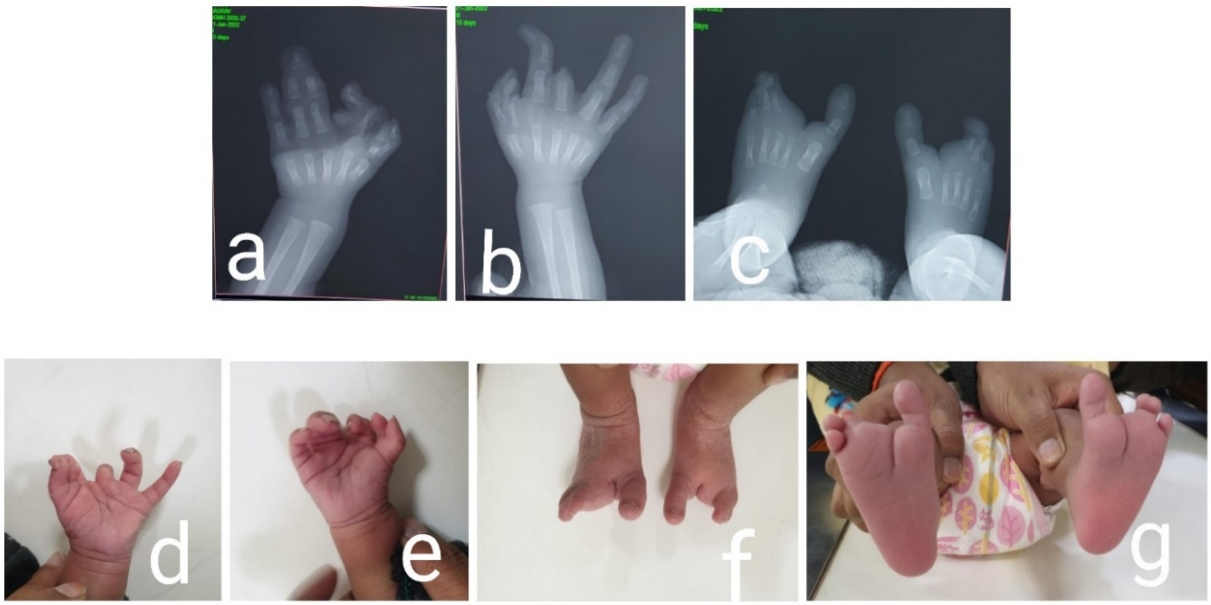

Figure 2. The clinical picture shows Bilateral feet with midline cleft with aplasia of the second toe, and fusion of the third and fourth toes (f, g). The bilateral hand shows midline cleft with syndactyly of third and fourth fingers with extra finger beside thumb on right hand and aplasia of the third finger on the left hand (d, e). Antero-posterior radiographs show all the metacarpals and metatarsals are normally developed with aplasia, syndactyly, and polydactyly seen in the toes and fingers (a, b, and c).

Further revelations it was observed that the paternal grandmother of an affected child also suffered from bilateral cleft feet (Figure 3).

She was the 5th child of their parents.

At the birth, her mother was 35 years of age.

The deformity was noted since birth but parents never sought any medical intervention in any form to treat the deformity.

Later on, as the child started growing it was not possible to accommodate widened feet in any footwear hence parents started tying forefeet to alter the shape of feet synonyms with the Chinese tradition of foot binding.

The Patient's mother has counseled regarding the functionality and aesthetic of the deformed limb through the prosthesis and reconstruction surgery to improve function and appearance.

A written inform consent was obtained from the caregivers prior to the publication of these data.

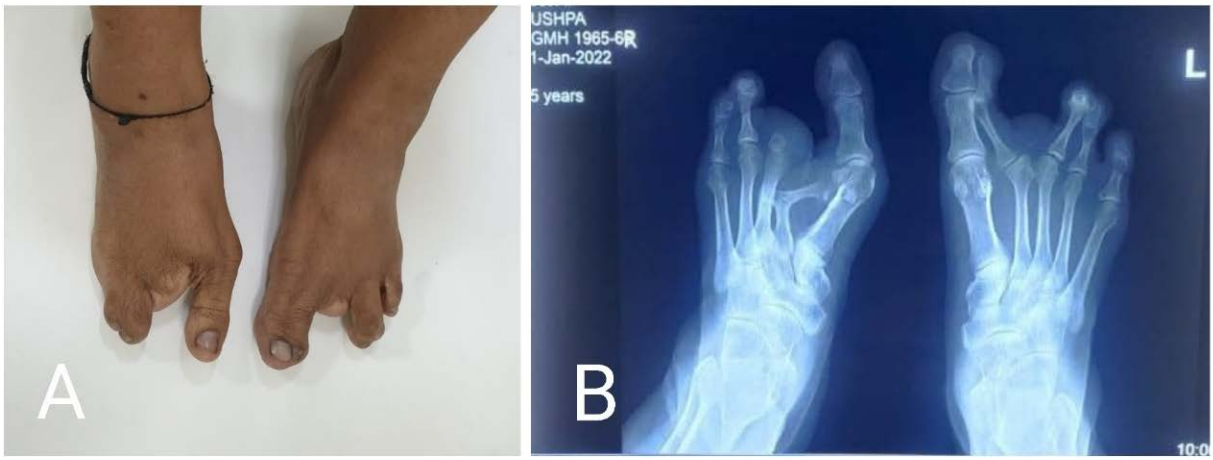

Figure 3. The Clinical image of case 2 shows split foot malformation with midline cleft (A), Antero-posterior radiograph of the bilateral foot shows bilateral cleft feet with aplasia, syndactyly of toes.

Discussion

Split-hand/foot malformation (SHFM) is a congenital limb developmental malformation, characterized by a variable degree of deep median clefts of the hands and/or feet due to the absence of central rays of extremities (also known as ectrodactyly) and metacarpal, metatarsal, and phalangeal aplasia or hypoplasia [3].

SHFM is inherited as an autosomal dominant, recessive, or X-linked entity, with a prevalence of 1 in 90,000 live births, and its clinical severity differs from patient to patient as well as between the limbs of the same patient [2].

SHFM accounts for 8 to 17% of all limb malformations.

The incidence of isolated SHFM is approximately 1:18000 births, of which 80% have only one affected limb with upper limb predominance [4].

In our second case, we only have bilateral split foot malformation rather than SHFM without syndromic association.

SHFM can be inherited or sporadic. Inheritance is mostly autosomal dominant with intra-familial clinical variability, and Sporadic cases can be caused by de novo mutation/chromosome imbalances.

The condition can be clinically and genetically heterogeneous and shows predominantly autosomal dominant inheritance with varying expressivity and reduced penetrance.

The autosomal dominant mode of inheritance is typical for SHFM1, SHFM3, SHFM4, SHFM5, SHFLD1, SHFLD2, SHFLD3.

Autosomal recessive and X-linked inheritance is very uncommon and has been noted only in a few families.

In addition, there are three genes TP63, WNT10B, and DLX5 which are noted to convey point mutations in patients affected by SHFM.

A large number of human gene faults can lead to SHFM.

Autosomal-dominant with reduced penetrance is the most common mode of inheritance.

Anticipation has been suggested in some families.

Autosomal-recessive and X-linked forms occur more rarely and other cases of SHFM are caused by chromosomal deletions and duplications [5-7].

Considering the pathophysiology of variable expression, reduced penetrance, non-mendelian inheritance, and segregation falsification [8], genetic counseling, correct molecular diagnosis, and prenatal testing in SHFM cases are difficult and extremely challenging.

Moreover, variability of the phenotype between affected individuals of the same family makes it very challenging to diagnose the exact molecular etiology.

Table 1. Clinical phenotypes associated with SHFM types.

SHFM Types	Inheritance	Causative genes/ molecular mechanism	Phenotypes
SHFM 1a	AD	DLX5, DLX6 mutation	Ectrodactyly, split hand, aplasia of single digital ray, hypoplasia, triphalangeal thumbs, lower limbs with broad hallux and clinodactyly.
SHFM 1b	AR	DLX5 mutation	Sensorineural hearing loss, short stature, mild scoliosis, split hand/foot, cylindrical nails.
SHFM 2	XL	Xq26	Split hand/foot, monodactylous median cleft anomaly, partial syndactyly, metacarpal and phalangeal hypoplasia.
SHFM 3	AD	10q24	Maxillary hypoplasia and micrognathia, dysplastic ears with hearing loss, cleft palate, renal anomalies, ectrodactyly, clinodactyly, ridged and dystrophic nails, intellectual disability in some patients.
SHFM 4	AD	TP63 mutation	Split hand/foot, missing phalanges, monodactyly, triphalangeal thumb, syndactyly, missing metacarpals and metatarsals.
SHFM 5	AD	2q31	Monodactyly, penoscrotal hypoplasia, growth retardation, hypertelorism, cleft palate, microcephaly, microphthalmia, split hand malformation.
SHFM 6	AR	WNT10B mutation	Ectrodactyly, with variable syndactyly and polydactyly also reported.
SHFM 7	AR	ZAK mutation	Split foot malformation, normal hands, hearing impairment, cutaneous syndactyly, and duplication of finger nail bed of fourth digit.
SHFM 8	AR	EPS15L1 microdeletion	Mild-sever split foot, missing metacarpals and metatarsals, complex preaxial syndactyly, underdeveloped digits and missing nail.
SHFLD 1	AD	1q42.2q43	Cleft hand, absent tibia, absent middle finger, tetramonodactyly, transverse hemilalia, hypoplastic big toe, bifurcation of femur, cup shaped ear, ulna hypoplasia/aplasia.
SHFLD 2	AD	6q14.1	Mild-severe skeletal defect of upper and lower limbs, split hand/foot, syndactyly of finger/toes, hypoplastic big toes, absence of middle finger, hypoplasia of tibia, beaked nose, no cleft lip/palate, or ectodermal dysplasia.
SHFLD 3	AD	BHLHA9 microduplication	Ectrodactyly, oligodactyly, brachydactyly, syndactyly, camptodactyly, pes varus, club foot, tibia hypo/aplasia, femoral bifurcation.

Note: AD, autosomal dominant; AR, autosomal recessive; XL, X-linked;
SHFM, Split hand-foot malformation, SHFLD, Split hand-foot malformation with long bone deficiency.

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In most of the isolated single cases with SHFM, conventional karyotyping can recognize large chromosomal aberrations and thus reveal the disease phenotype.

Twelve different types of SHFM have been mapped to different human chromosomes, including SHFM1(a,b), SHFM2, SHFM3, SHFM4, SHFM5, SHFM6, SHFM7, SHFM8, SHFLD1, SHFLD2, and SHFLD3 [9] (Table 1).

Patients presenting with SHFM options ought to be rigorously diagnosed, clinically examined, and submitted to relevant cytology and/or molecular testing.

Firstly, the clinician should take an appropriate history including detailed family history with a pedigree chart and proper examination from head to toes.

Then, the related investigation includes radiographs, karyotyping, relevant cytological and molecular testing.

Genetic counseling would help the family to understand the genetic nature of the disease and develop proper risk management strategies for the disease.

Management of cases of SHFM is aimed at improving the functionality and aesthetics of the affected limbs through prosthetics and reconstructive surgeries [10].

SHFM can be detected as early as the 13th week of gestation by three-dimensional ultrasonography.

Screening of candidate genes has also been suggested for high-risk families with help of Antenatal genetic diagnostic tests.

But, the commercial accessibility of genetic testing is limited [11].

During the genetic counseling session, the patient's parents were counseled in detail about the nature of the disease, and the various modalities available for its early detection, prevention, and management and possibility of recurrence of abnormality in future siblings.

Conclusions

The clinical and genetic heterogeneity of SHFM contributes to extremely challenging and difficult genetic counseling.

Genetic alteration and proper molecular diagnosis responsible for SHFM are important for the entire family.

Firstly, genetic counseling would help the family to understand the genetic nature of the disease and develop proper risk management strategies for the disease, and also facilitate conscious family planning and support the prenatal or preimplantation diagnosis.

So, Clinicians should be making a proper molecular diagnosis, providing a precise recurrence risk assessment, and developing a management plan for the well-being of patients and their family.

Conflict of interests

None to declare.

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