A Case Report of Fetal Split Hand Foot Malformation Syndrome: A Rare Congenital Limb Anomaly

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Abstract

Fetal split hand foot malformation (SHFM) syndrome is a rare congenital disorder characterized by developmental abnormalities of fingers and/or toes, resulting in a split appearance. SHFM is sporadic and shows mainly autosomal dominant inheritance with variable clinical presentation. Prenatal diagnosis plays a crucial role in the management and in counseling of affected families. In this case report, we present the diagnosis of SHFM through ultrasound imaging and genetic testing in a primigravida, along with post abortal fetal findings. The aim was to highlight the importance of early detection during routine ultrasound and genetic counseling for appropriate understanding and management of this rare limb condition.

Keywords

- split hand foot malformation syndrome
- prenatal diagnosis
- ultrasound
- genetic testing
- whole exome sequencing

Introduction

Fetal split hand foot malformation (SHFM) syndrome, also known as ectrodactyly, is a rare genetic disorder characterized by the absence or malformation of the central rays of the hands and/or feet.[1] It is a heterogeneous condition with variable clinical presentations and inheritance patterns. The etiology of SHFM syndrome involves genetic and environmental factors, making accurate diagnosis and genetic counseling essential.[2] Early prenatal diagnosis of SHFM is crucial for providing relevant information to parents, offering genetic counseling, and enhancing understanding of deformities, thus enabling appropriate medical intervention.

Case Report

We present the case of a 33 year old primigravida woman who conceived after 5 years of nonconsanguineous marriage. She came to us at approximately 22 weeks of her pregnancy and underwent a routine mid trimester ultrasound examination. She had no previous scans. The patient had no family history of congenital anomalies. The ultrasound revealed bilateral limb anomalies characterized by the absence of a few phalanges (central rays) of both hands and feet, consistent with the diagnosis of fetal SHFM syndrome. The remaining digits also appeared abnormal in structure and length. No other associated anomalies were detected in the fetus. Ultrasound images are presented here to demonstrate the key features of the case in two dimensional mode (►**Fig. 1A** and **B**), four dimensional volume contrast imaging A plane skeletal mode (►**Fig. 2A** and **B**), and three dimensional surface rendering mode (►**Fig. 3A** and **B**).

The utilization of ultrasound imaging in the diagnosis of fetal SHFM is crucial. The images provide valuable visual evidence of the limb anomalies, aiding in accurate diagnosis.

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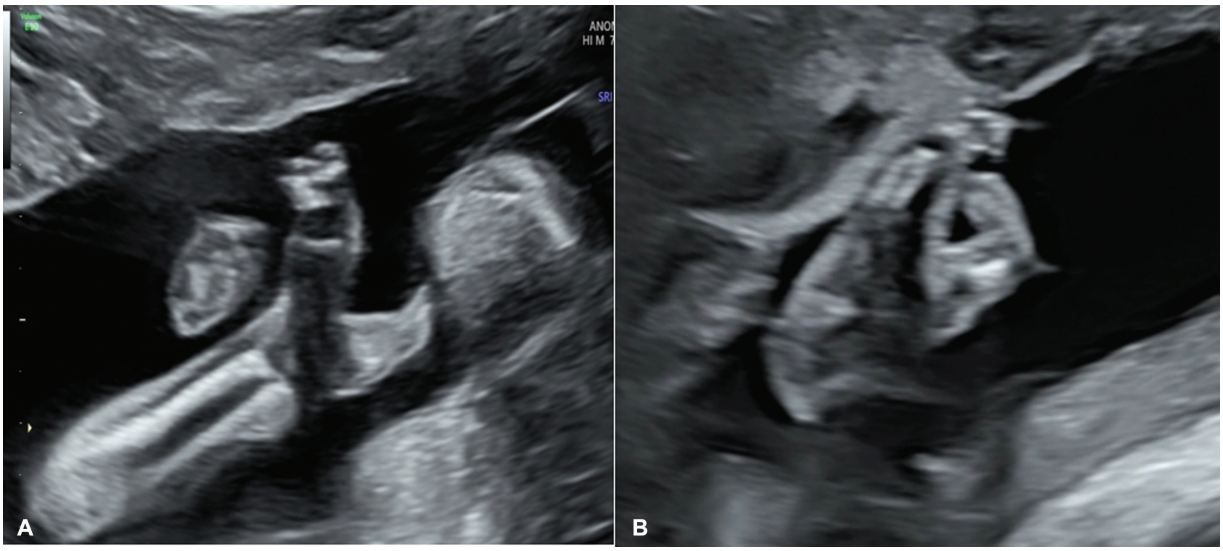

Fig. 1 Two dimensional (2D) ultrasound image revealing the absence of central phalanges in fetal hand (**A**) and in fetal foot (**B**).

Ultrasound allows for the early detection of limb malformations and facilitates appropriate counseling for affected families. Furthermore, the detailed ultrasound assessment enables a comprehensive evaluation of the extent and severity of limb involvement, which guides the subsequent management strategy and long term prognosis.

Further investigations, including genetic testing and counseling, were initiated to confirm the diagnosis and provide appropriate management options.

To confirm the suspected diagnosis of SHFS, the patient underwent genetic testing. Amniocentesis was performed to obtain amniotic fluid for whole exome sequencing. Fetal deoxyribonucleic acid was extracted, and targeted genetic sequencing was performed to identify mutations in genes associated with SHFS, including the TP63 gene. Genetic analysis confirmed a heterozygous variant in the TP63 gene of unknown significance. The mutation variant of TP63, 926A > G, Asn309Ser (►**Fig. 4**) is predicted as damaging. This gene encodes a member of the p53 family of transcription factors, and it is well known that mutations in this gene are associated with SHFM, among other genetic disorders.[3,4] The parents got recommendations from a genetic counselor for undergoing parental genetic testing based on the genetic report. They denied the same, because of financial constraints.

All possible options for postnatal treatment were presented to them and counseled in a nondirective, nonjudgmental way. The final decision by the parents was to go for termination, noting that all four limbs were involved and surgical correction with complete functional recovery cannot be guaranteed, apart from the financial liability associated with the treatment. Termination was done by the local referring doctor before the completion of 24 weeks after obtaining the necessary informed consent.

Post Abortal Findings

Following the termination of pregnancy, gross examination of the fetal limbs (►**Fig. 5A–D**) revealed bilateral absence of the central digits (digits II–III) in both hands and feet,

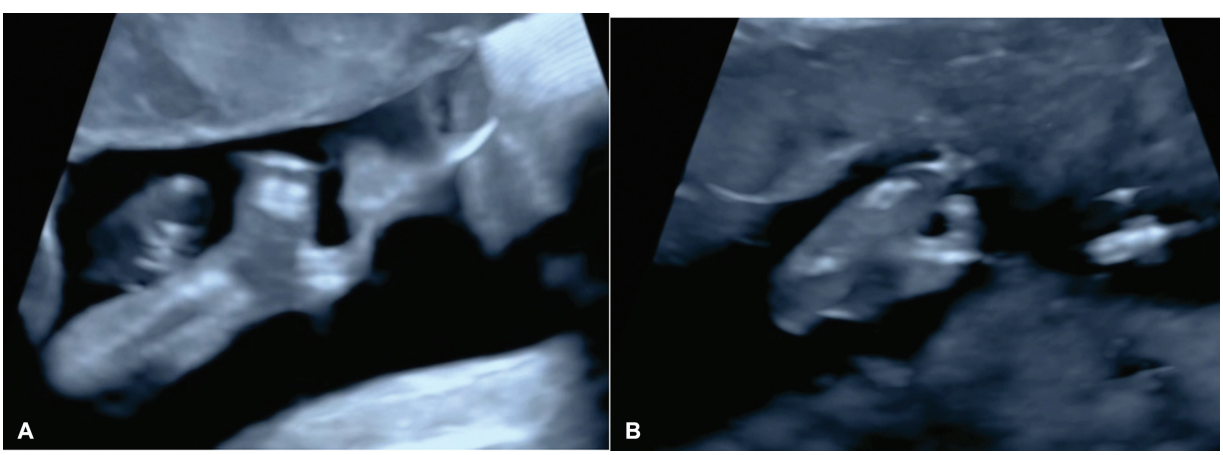

Fig. 2 Four dimensional volume contrast imaging (4D VCI) skeletal mode ultrasound showing loss of central 2 digits and syndactyly of 4th and 5th digits in fetal hand with very short proximal phalanges in remaining digits (**A**) and cleft foot with syndactyly of 1st and 2nd toes along with absent proximal phalanges (**B**).

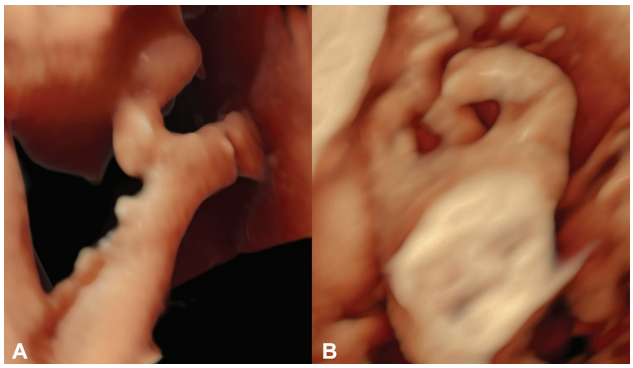

Fig. 3 (3D) ultrasound surface rendering mode showing typical cleft appearance of fetal hand (**A**) and fetal foot having "crab"-like appearance (**B**).

consistent with the prenatal ultrasound findings. Visual examination also confirmed syndactyly and short distal phalanges, as seen in prenatal ultrasound imaging of both the hands and feet.

Discussion

Fetal SHFM is a rare limb abnormality with an estimated incidence of 1 in 90,000 births,[3] although the incidence varies as per different medical literatures. It is a genetically heterogeneous condition that can be inherited in an autosomal dominant, autosomal recessive, or X linked manner and can occur sporadically.[4] Several genes have been associated with SHFM, including TP63, WNT10B, and DLX5, among others.[5] This is a rare condition with high complexity due to the clinical variability and sometimes unpredictable genetic inheritance observed in the affected individuals.[6] According to genetic features, 12 different types of SHFM have been classified and linked to genetic aberrations in different human chromosomes.[6] Prenatal diagnosis is crucial for appropriate counseling, as it allows families to make informed decisions regarding pregnancy management and potential treatment options. Prenatal diagnosis of SHFM is typically based on ultrasound findings, which may include the absence or malformation of the central digits. In cases where the diagnosis is uncertain, genetic testing can provide

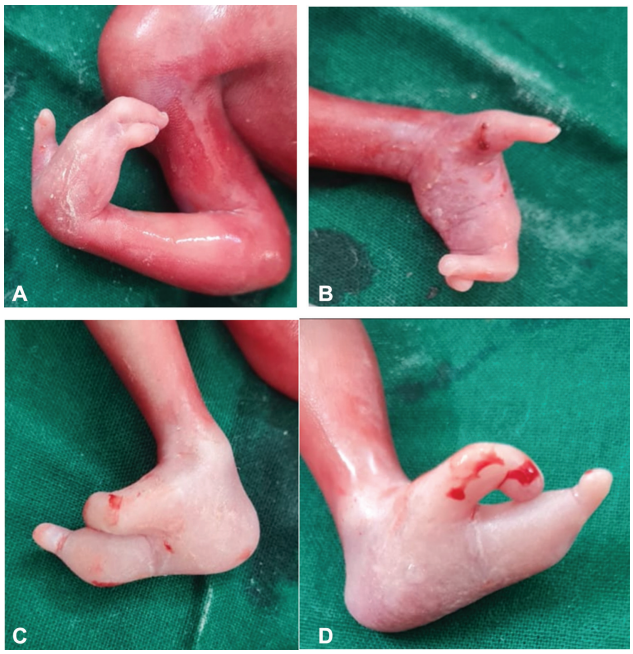

Fig. 5 (**A**) Right hand of abortus. (**B**) Left hand of abortus. (**C**) Right foot of abortus. (**D**) Left foot of abortus.

confirmation and identify the specific genetic mutation involved.

Prenatal ultrasound has limitations in accurately detecting SHFM during early gestation. However, a thorough examination at 18 to 22 weeks of gestation can usually reveal the characteristic findings. Suspicion for SHFM may be there if the following features are found during routine fetal ultrasound examination:

1. Absence of one or more fingers or toes.
2. Splitting or having cleft of the hand or foot, resulting in a "lobster claw" appearance.
3. Malformation or fusion of fingers or toes.
4. Differences in the size or shape of the fingers or toes.

The absence or malformation of the central digits and the preservation of the lateral digits are important clues to diagnosing SHFM. Prenatal diagnosis allows parents to make informed decisions regarding their pregnancy,

Gene&Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classifcation
TP63 NM_003722.5	c.926A>G p.Asn309Ser	Exon 7	Heterozygous	CADD: 24 SIFT: Tolerated; Polyphen2: Damaging MT: Damaging	SPLIT-HAND/FOOT MALFORMATION 4;SHFM4;605289	Autosomal Dominant	Uncertain Significance
FLNB NM_001457.4	c.1954G>C p.Gly652Arg	Exon 13	Heterozygous	CADD: 26.1 SIFT: Tolerated; Polyphen2: N/A MT: Damaging	ATELOSTEOGENESIS, TYPE I; AO1;108720	Autosomal Dominant	Uncertain Significance

Variant 1, TP63,926A>G, Asn309Ser
This gene encodes a member of the p53 family of transcription factors. The functional domains of p53 family proteins include an N-terminal transactivation domain, a central DNA-binding domain and an oligomerization domain. Mutations in this gene are associated with ectodermal dysplasia, and cleft lip/palate syndrome 3 (EEC3); split-hand/foot malformation 4 (SHFM4); ankyloblepharon-ectodermal defects-cleft lip/palate; ADULT syndrome (acro-dermato-ungual-lacrimal-tooth); limb-mammary syndrome; Rap-Hodgkin syndrome (RHS); and orofacial cleft 8.
This is a 680 amino acid protein, the identified variant is **within DNA-binding domain** of the protein (156-356 amino acid). Minor allele frequency is 0%. The variant is predicted as damaging

Fig. 4 The (WES) report showing relevant mutation of TP63 gene related to split hand/foot malformation.

including potential interventions and the need for specialized medical care after birth.

Post birth reconstruction of affected limb deformities is the mainstay of the therapeutic approach. The success rate of reconstructive surgery for SHFM can vary based on individual factors, severity of malformations, and the specific surgical procedures performed and thus outcomes can differ significantly.

Success rates depend on the type of SHFM, the extent of limb involvement, and the patient's overall health. Reconstructive surgical closure of the central cleft is often performed to improve hand and foot function. Creating functional spaces between digits can enhance dexterity and the creation of functional digits (fingers or toes) is done using available tissue. Early surgical interventions contribute to better functional outcomes. Hand and foot physiotherapy is part of the rehabilitation process. Psychological support is essential.[7,8]

The inclusion of post abortal findings in this case report provides additional insights into the appearance of limbs associated with SHFM. Genetic counseling is an essential component of diagnosis for SHFM. In our case, the identification of a heterozygous variant in the TP63 gene reveals the genetic basis of the condition. Genetic counseling was provided to the parents, explaining the inheritance pattern, recurrence risk in future pregnancies, and the availability of prenatal genetic testing options.

Conclusion

Fetal SHFM syndrome is a rare congenital limb deformity with significant physical and psychological implications for affected individuals and their families. Diagnosis in early pregnancy is crucial for appropriate counseling and management. Ultrasound is the main imaging modality for prenatal diagnosis with the need for a high index of suspicion for this rare condition. Genetic testing and counseling should be offered to affected families to determine the underlying genetic cause and facilitate informed decision making regarding future pregnancies. More research is warranted to improve our understanding of the pathogenesis, diagnosis, and treatment options for this rare condition.

Conflict of Interest
None declared.

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