Case Report

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Gynaecology & Obstetrics Case report
ISSN 2471-8165

2021
Vol.7 No.10:163

Harlequin Ichthyosis: Prenatal Diagnosis of a Rare Genetic Dermatosis

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Abstract

Harlequin foetus otherwise called as ichthyosis is a rare disorder which affects the foetus and transmitted through autosomal recessive inheritance. Incidence of the disease is nearly 1 in 2,00,000 to 3,00,000 live births. The affected foetus usually dies at birth and most often they are born pre-term. Harlequin Ichthyosis (HI) is characterized by severe keratinisation and alligator-like horned skin disorder. HI is associated with mutation in the ABCA12 gene. It recurs and family history and plays a major role. Therefore, genetic counselling and screening for mutation of this gene should be considered. Prenatal testing with amniocentesis and USG in late second trimester will help to diagnose the condition. ART and PGT will help to diagnose this genetic disorder.

Keywords: ABCA12 gene mutation; Autosomal recessive; Skin abnormalities

Received: September 15, 2021; **Accepted:** October 06, 2021; **Published:** October 13, 2021

Citation: Thirunavukkarasu R (2021) Harlequin Ichthyosis: Prenatal Diagnosis of a Rare Genetic Dermatosis. Gynecol Obstet Case Rep Vol.7 No.10:163

Introduction

Harlequin Ichthyosis (HI) is an extremely rare genetic skin disor and it may be lethal [1,2] or the victims may rarely survive several months or few years with extreme medical attention It is an autosomal recessive disorder characterized by congei epidermis abnormality [4,5]. Majority of affected individ being homozygous for mutation in the *ABCA12* gene.

Incidence is 1 in 2,00,000 to 300,000 [6]. The phenot continuum of classic lamellar ichthyosis and non-bul congenital Ichthyosis formerythroderma, self-healing collo infant, acral self-healing collodion baby, bathing suit ichthy and harlequin ichthyosis are all included in Autosomal Reces Congenital Ichthyosis (ARCI).

The mode of inheritance is autosomal recessive or X-linked [7]. Til date, mutations in at least six genes have been identified [5]. Ir suspicious cases, fetal skin biopsy, electron microscopy and DNA-based diagnosis with chorionic villus sampling or amniocentesis can be used to validate the antenatal diagnosis [8]. HI is the most severe type of ichthyosis. It is characterized by thickened dry, rough and armor like plates of skin with deep cracks in between. Other clinical features include ectropion, eclabium, open mouth, polydactyly, syndactyly, small and swollen hands and feet, hypo-plastic fingers, anonychia, lack of development of external parts of nose and ears, fusion of ears to the head, breathing difficulty due to tight chest skin, decreased mobility and flexion of joints [2-5]. The lethal outcome of Harlequin Ichthyosis is due to the development of sepsis, respiratory failure, hypothermia, hyperthermia, malnutrition and dehydration [2,9].

Pre term birth is common and death occurs due to dehydration, respiratory failure, hypothermia, hypo-glycaemia, renal failure and sepsis [3]. In older children, sparse or thin hair as a result of scales on the scalp, unusual facial features, hard of hearing, recurring skin infections are common.

Diagnosis and testing

The diagnosis of non-syndromic ARCI is established by skin findings at birth and infancy. Skin biopsy is not necessary to establish the diagnosis of ARCI. The twelve genes known to be associated with ARCI are *ABCA12, ALOX 12 B, ALOX E3, CASP 14, CERS3, CYP4F22, LIPN, NIPAL 4, PNPLA1, SDRC9C7, SLC27A4* and *TGM1*. At least 15% of the affected families do not have the pathogenic variants in any of the known genes. Chromosomal Micro Analysis (CMA) and Whole Exome Sequencing (WES) is possible through amniotic fluid analysis.

Management

For neonates, moist environment is an isollette, hygienic handling to prevent infection and treatment of infections are important. Petroleum based creams or ointments to keep skin soft, supple

and hydrated can be used. Prevention of secondary infection, dehydration and overheating, corneal drying and high calorie diet are mandatory to save the new born. Surveillance should be regular physical examination for evidence of infection, management of skin involvement as well for the increased risk of skin malignancy.

Case Report

A 28 years old female with gravida 2 para 1 and live 0, presented with history of early neonatal death of the first baby. There was no H/O consanguineous marriage and she presented to us at six weeks of pregnancy for routine antenatal checkup. During her first pregnancy she had delivered a preterm baby at 36 weeks due to PPROM and emergency LSCS was done in view of non-progression of labor. She delivered a live male baby with birth weight of 2.2 kg, cried well after birth. Infant had clinical features of ichthyosis with thick skin with deep fissures, general hyper-keratinization, ectropion and eclabion and died on Day 7 of life.

The couple had undergone whole exome sequencing. Test results revealed both the parents were found to harbour a heterozygous variant of uncertain significance on Exon 11 in *ALOX 12B* gene which is associated with ichthyosis autosomal recessive trait. In addition, the mother was found to be a carrier for a heterozygous pathogenic mutation in FKTN gene and IVD gene which are associated with muscular dystrophy and isovaleric academia respectively. The husband was not found to be the carrier for any pathogenic variants in FKTN and IVD genes.

In her present pregnancy routine antenatal investigations were done, which were found to be normal. Patient underwent first trimester screening at 12-13 weeks. She was screen nega for Down's syndrome, Edward's and Patau's syndrome. was advised to undergo early second trimester scan at 18 weeks and the baby was found to be anatomically nor Amniocentesis was done to look for the heterozygous variar unknown significance on *EXON11* in *ALOX12B* gene.

The parent's blood sample and the amniotic fluid sample v analyzed using PCR followed by DNA sequencing for the targ variant in the *ALOX12B* gene that was observed in prev affected child. Couple was found to be having heterozyg variant of unknown significance on *EXON11* in *ALOX12B* gene. fetal DNA was homozygous for the same gene, which predicts high chance of the fetus being affected. Genetic counselling done and the couple opted for termination of pregnancy.

Discussion

The first case report of a similar disorder was presented by Hart in South Carolina, United States of America, at 1750 [10]. Harlequin Ichthyosis is an infrequent genetic disorder with an incidence of 1 in 300,000 live births [6]. Fetuses of consanguineous marriages are prone to develop Harlequin Ichthyosis. Mutations in the **ABCA12** gene have been reported in the majority of HI patients [4,9]. Mutation in the ABC transporters, *ABCA12* a cell membrane transporter concomitant with lipid transportation are considered to be the underlying pathogenesis for Harlequin Ichthyosis. The new born affected by this mutation have defective lipid secretion within epidermal keratinocyte resulting in loss of skin lipid barrier and progression to Harlequin Ichthyosis. Chances of survival depend on the type of mutation. Homozygous variant has poor survival compared to heterozygous gene mutation.

This gene plays a major role in transporting lipids to cells that form the epidermis and the normal development of the skin [2]. At birth, infants are covered with hard hyper-keratotic armour, composed of large, thick, yellowish brown, and very sticky plates [9,10]. After birth, deep red fissures occur on these hard and inflexible plates that extend to the dermis, resulting in a joker-like skin. Infants with HI might have microcephaly, ectropion, and eclabium [4]. External auditory meatus and nostrils appear rudimentary and immature [5]. In addition, patients with HI have respiratory failure as a result of restricted chest expansion and skeletal deformities. Feeding problems may result in low blood sugar, dehydration, and kidney failure. In addition, temperature instability and infection would be common [4,9]. Almost all these clinical features were observed in the current case. In the present case the first baby was diagnosed to have Ichthyosis but genetic testing was not done. Hence couple underwent exome gene sequencing and found to harbour heterozygous variant of unknown significance on *EXON11* in *ALOX12B* gene.

As the patient underwent early target scan at 17 weeks, ultrasound features of ichthyosis could not be picked up. Since it is difficult to diagnose fetal Harlequin Ichthyosis, genetic testing and counselling becomes imperative. USG shows dentofacial deformity like eversion of eye lids, lips, thick palm, plantar soft tissues, short foot length, incurved toes, clinched fist, poor delineation of nostrils and polyhydramnios [10]. Furthermore, where a DNA diagnosis is inaccessible, these scans may be helpful [6]. Amniocentesis was done during this pregnancy to look for the same defect.

Family history of Ichthyosis births, history of consanguinity, previous pregnancy history are high risk factors. A skin biopsy is likely show anatomical defects of lamellar granules and epidermal keratin expression in the postnatal diagnosis. The grotesque presentation of the fetus is usually enough to make a diagnosis [10]. HI was instantly diagnosed at birth due to its extreme clinical characteristics. In subsequent births, the rate of recurrence was more than 20%. However, with the advancement in prenatal testing procedures, few cases of HI with a family background had been diagnosed prenatally, and the parents had undergone adequate counselling leading up to the births of the babies [5].

Management during early neonatal period includes, multidisciplinary approach**,** humidified incubator to prevent the dehydration**,** physiotherapy for contractures, analgesics for deep fissures**,** antibiotics and adequate nutrition. The mortality of HI is high and most of the neonates die within a few weeks of birth because of secondary complications such as infection and dehydration [4]. However, survival contributes to the type of mutations; neonates with the compound heterozygote mutation survive more than those with the homozygote mutation [10]. The mortality of HI is high and most of the victims die within a few weeks of birth because of secondary complications such as infection and dehydration [4]. However, survival contributes to

the type of mutations; victims with the compound heterozyg mutation survive more than those with the homozyg mutation. In addition, advances in the postnatal treatments cares improve the prognosis of the disease [4,10]. The surv rate increases to more than 50% with early prescription of retinoids. The patients' quality of life improves with suppor cares. In addition to the routine care such as checking vital si patients should be kept in a warm and humid incubator. Hydra should be performed [11]. As accessing to the peripheral ves can be difficult, an umbilical venous catheter might be nee Taking shower twice per day, saline compresses and ge emollients must be used to keep the skin soft and to accele the desquamation. Water and electrolyte disturbances mus managed as well. Environment must be cleaned up to prev infection; hence, repeated cultures of the skin would be esse to detect the hazardous micro-organisms [4]. In addition, ger counselling and molecular investigation of the **ABCA12** gene performed.

Families with one or more children with HI have been previo reported. Another study has reported two cases with HI f Mashhad, Iran [11]. The first case was a 2.0 kg premature girl was delivered at 32 weeks of pregnancy and died 3 days a birth. She was the product of a first-cousin marriage. The sec one was also a girl with a weight of 2.3 kg [12].

Conclusion

Harlequin Ichthyosis is a lethal skin condition. Genetic counselling of parents should be done in families with history of consanguineous marriage along with prenatal screening for particular mutated gene mainly *ABCA12B*. Early diagnosis of Harlequin ichthyosis and genetic counselling may decrease the stress to family. Also, Assisted Reproductive Technologies (ART) followed by Pre-Genetic Diagnosis (PGD) is recommended in subsequent pregnancies to find out the recurrence of the disease which can reduce the stress of the family. Termination can be offered in such situations. Neonates with HI are likely to have a stormy neonatal period and their life span is short lived. The family needs social and psychological assistance. Invariably the new born dies due to fulminant neonatal sepsis. Prevention of dehydration, infection, managing skin conditions and physical therapy can help to improve the neo natal outcome. This case is presented as it is a rare case and there is recurrence of the condition. Moreover, it has occurred for the couple out of non-consanguineous marriage and this abnormality has been diagnosed in utero and termination was done earlier. Since the couple harbors the genes for HI, there are chances of recurrence in subsequent pregnancies. They are advised ART with embryo donation.

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