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Case Report

Neonatology Section

Genetic Counselling and Prenatal Diagnosis in a Case of Harlequin Ichthyosis: A Novel ABCA12 Gene Mutation

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ABSTRACT

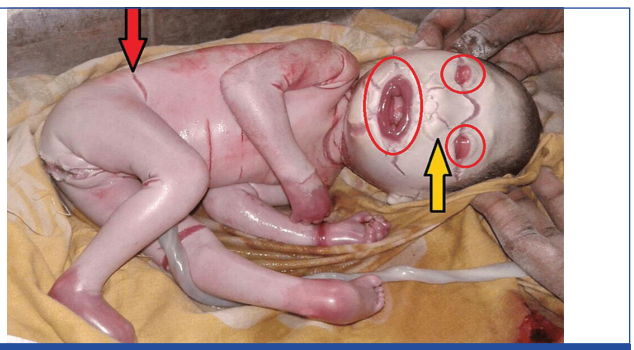
Hereditary diseases are disorders that mainly result from mutations or changes in Deoxyribonulciec Acid (DNA), Ribonucleic Acid (RNA), or chromosomes, which impact the overall and physical welfare of an individual. One such severe inherited skin disease is Harlequin Ichthyosis (HI), which is characterised by the rigid and thick formation of diamond-shaped scales on the skin. It occurs due to a mutation in the ABCA12 gene, which plays a central role in the formation of the outermost layer of the skin. Hereby, the authors present a case of a 29-year-old female presented herself at Acharya Vinoba Bhave Rural Hospital (AVBRH) for hereditary counselling. She was 38 weeks pregnant and had no other chief complaints; however, she wanted proper counselling for the pregnancy due to the death of her previous children. In her prior pregnancy, the neonate was diagnosed with HI and exhibited all the manifestations of grossly thick, inelastic skin, which posed a high risk for life-threatening complications, including infections, fluid loss, and episodes of acute respiratory intolerance. The neonate was born at 40 weeks of gestation. Other initial diagnostic methods, such as amniocentesis, Chorionic Villus Sampling (CVS), and pre-implantation genetic diagnosis during In-vitro Fertilisation (IVF) for genetic disorders, were utilised. These prenatal testing techniques facilitate genetic screening methods in managing hereditary ailments such as HI in present case. Genetic testing revealed that both parents carried a heterozygous deletion in the ABCA12 gene, indicating a 25% chance of having another affected child. Early identification of the disease and its treatment will enable neonates to have the best quality of life possible.

Keywords: Amniocentesis, Hereditary skin disorders, Preimplantation diagnosis, Prenatal genetic screening, Recessive genetic conditions

CASE REPORT

A 29-year-old female presented herself for hereditary counselling. She was 38 weeks pregnant and had no other chief complaints; however, she wanted proper counselling for the pregnancy due to the death of her previous children. She had a history of a second-degree consanguineous marriage, which is related to an increased risk of autosomal recessive disorders in such unions. Her obstetric history is notable for having Gravida 3, Para 2, with no live children (G3P2L0). She has had one ectopic pregnancy and a newborn death at 40 weeks of pregnancy due to respiratory distress. Aside from pregnancy complications, the patient has no significant medical or surgical history. In her previous pregnancy, she delivered a child diagnosed with HI, a severe and rare genetic skin disorder.

This disorder is characterised by thicker skin and severe abnormalities, such as a flat nose, eyelids and mouth turned inside out, and fissures separating plates of hard, thick skin. These features frequently result in premature infant mortality due to complications such as dehydration, infection, and respiratory distress. The typical traits that supported the child's visual and clinical diagnosis of HI has been depicted in [Table/Fig-1].



[Table/Fig-1]: Harlequin Ichthyosis (HI) typical traits.

The given figure illustrates the typical traits that supported the child's visual and clinical diagnosis of HI. A yellow-coloured arrow indicates a flat nose, while the eyelids and mouth turned inside out are encircled in red. Fissures separating the plates of hard, thick skin are also shown by the red-coloured arrow. Given her history and the previous affected child, the patient underwent genetic testing to understand the underlying cause of the disorder. The case revealed a gene mutation in the ABCA12 gene, specifically a heterozygous deletion of c.6368delC (p.S2123fs*22) in exon 41. This mutation induces a frameshift, leading to the occurrence of a premature stop codon, and is deemed deleterious. The genetic findings confirmed the diagnosis of Ichthyosis autosomal recessive 4B (Harlequin) and Ichthyosis congenital autosomal recessive 4A (OMIM ID: 607800). The HI is known to be caused by biallelic mutations in the ABCA12 gene, which plays a critical role in the formation of the skin barrier. Subsequent genetic testing was performed on the patient's husband, revealing that he also carries the same heterozygous deletion within the ABCA12 gene. Both parents are carriers of the ABCA12 gene mutation; other family members may carry the same alteration, but no genetic testing has been done on them. This was confirmed through focused transformation examination utilising Polymerase Chain Reaction (PCR) and sequencing techniques, which showed both the patient and her spouse as carriers of the same pathogenic variation.

Given that both parents are carriers of a pathogenic mutation within the ABCA12 gene, there is a 25% chance with each pregnancy that the embryo will acquire both mutated alleles, leading to HI. This significant risk required detailed genetic counselling for the couple, centering on the implications of their carrier status and discussing potential management strategies for future pregnancies. Several reproductive options were presented to the couple to help them manage the risk of having another child with HI. One option presented was prenatal diagnosis, which involves testing

during pregnancy to determine if the embryo has acquired the pathogenic variants. Methods such as CVS or amniocentesis can be performed, typically in the first or second trimester, respectively. These methods involve examining placental tissue or amniotic fluid to analyse foetal DNA, providing crucial information on whether the embryo is affected by the disorder. Although these tests carry a small risk of complications, they offer the benefit of early detection and informed decision-making.

Another option presented was Preimplantation Genetic Diagnosis (PGD), which is used in conjunction with assisted reproductive techniques like IVF. The PGD involves testing embryos for the specific genetic mutation before implantation, allowing for the selection of embryos that do not carry the disease-causing mutations. This approach reduces the risk of having an affected child and ensures that only healthy embryos are transferred to the uterus. While PGD offers significant advantages, it is also complex, expensive, and involves several steps, including ovarian stimulation, egg retrieval, and embryo biopsy.

In addition to these reproductive procedures, the couple was advised to consider carrier screening for family members. Since, both parents are carriers of a pathogenic ABCA12 mutation, other family members may also carry the same mutation. Genetic testing can identify carriers, providing them with valuable information about their genetic status and potential reproductive risks. This information can be especially important for siblings and other relatives who may be planning their own families.

The couple was provided with detailed information on all these options, including the methods involved, the associated risks and benefits, and recommendations for their future reproductive choices. Monthly follow-ups were conducted for a year for the counselling of the parents. This counselling aimed to support them in making informed decisions about their reproductive health and family planning.

DISCUSSION

Genetic diseases occur when genes undergo structural or functional changes due to harmful mutations, pathogenic variations, or an abnormal amount of genetic material [1]. These irregularities can cause a variety of medical complications, affecting many aspects of physical and physiological health. HI is a severe inherited skin condition characterised by thick, diamond-shaped scales that cover the entire body and resemble the patterns on a harlequin costume [1]. It is caused by mutations in the gene that produces ABCA12, a protein required for the formation of the skin's outer layer [2]. Newborns with HI typically have very tight, thick skin that restricts flexibility and may lead to serious issues such as dehydration, infections, and respiratory problems [1,3].

Prenatal diagnosis is the method of identifying potential health issues or abnormalities in a developing baby before birth [4]. Prenatal diagnosis can be performed through ultrasound imaging, blood tests, genetic testing, which includes amniocentesis or chorionic villus sampling, and other specialised techniques [4]. A small sample of placental cells is extracted for genetic analysis during CVS, a prenatal diagnostic method [4,5]. Another prenatal diagnostic technique is amniocentesis, which involves extracting a small volume of amniotic fluid from the foetus's amniotic sac for genetic testing and other analyses [5]. PGD can be a reproductive technique used during IVF cycles to test embryos for genetic defects before they are implanted in the uterus [6].

In the presented case, a 29-year-old pregnant female without any chief complaints presented at AVBRH for hereditary counselling. She is from a second-degree consanguineous marriage; her obstetric history is G3P2L0. She had one ectopic pregnancy earlier and also experienced a newborn death at 40 weeks of pregnancy. The prenatal report shows a modification in the ABCA12 gene. In her previous pregnancy, she delivered a child diagnosed with HI, a severe and rare genetic skin disorder.

A case detailed by Auriti C et al., describes a neonate born at 35 weeks of gestation via caesarean section due to Premature Rupture of Membranes (PROM), which offers some clinical similarities and contrasts with the presented case of the 29-year-old female with a history of delivering a child with HI [7]. Both cases highlight the significance of hereditary counselling and the importance of ABCA12 gene mutations in HI.

In the neonatal case, the infant displayed classic indications of HI, including thickened skin with keratotic scales, ectropion, eclabium, and dysmorphisms, and required prompt and intensive dermatologic and systemic management [7]. Hereditary testing confirmed compound heterozygosity within the ABCA12 gene, identifying c.4036delG and c.7444C > T variations [7]. Despite the severe initial presentation, appropriate treatment led to significant improvements, including the reduction and possible cessation of acitretin by 10 months of age.

Presented is the case of a 29-year-old female with a second-degree consanguineous marriage and a history of a severely irregular infant from a previous pregnancy. She was referred for genetic counselling following the diagnosis of HI in her child. Genetic testing revealed a heterozygous deletion of c.6368delC (p.S2123fs*22) in exon 41 of the ABCA12 gene, which was consistent with the changes observed in her and her partner, confirming the autosomal recessive inheritance pattern of the condition. Unlike the neonatal case, the woman herself did not present with any symptoms of HI but carried the mutation responsible for the disorder in her offspring [7].

Both cases emphasise the genetic etiology of HI and the importance of early genetic screening and counselling, especially in consanguineous marriages where the risk of autosomal recessive disorders is increased. The neonatal case highlights the critical role of prompt and ongoing therapeutic intervention in managing HI and its symptoms, while the case of the 29-year-old female underscores the preventive aspect of genetic counselling and the identification of carrier status in parents to inform future pregnancies [7]. Both scenarios illustrate the varied presentations and implications of ABCA12 mutations, emphasising the need for comprehensive genetic and clinical management to improve outcomes for affected individuals and their families.

In a case of the male neonate detailed by Heap J et al., his guardians were second cousins, whereas in the case of the 29-year-old female, she had a history of unusual pregnancies, including a previous child with HI [8]. This commonality underscores the significance of genetic counselling in consanguineous unions to manage and anticipate potential genetic conditions. The male neonate presented at birth with the classic features of HI: hyperkeratotic skin, severe ectropion, eclabium, rudimentary pinnae and nostrils, and digit fusion. His diagnosis was confirmed clinically by a pediatric dermatologist and supported by his characteristic appearance [8]. This case highlights the typical neonatal presentation and the prompt postnatal care required for HI, including intensive skin care, dietary support, and management of complications such as infections and limb contractures [8]. Despite his severe initial presentation, ongoing management with acitretin and multidisciplinary support has allowed him to achieve a relatively good quality of life at 12 years old, although he continues to face persistent dermatological and visual issues [8].

In contrast, the presented case of the 29-year-old female focuses on genetic testing and counselling after giving birth to a child with HI. Genetic analysis identified a novel frameshift mutation in exon 41 of the ABCA12 gene (c.6368delC, p.S2123fs*22), classifying it as a novel pathogenic variant. This genetic information is significant for the couple's reproductive planning and for understanding the genetic nature of the condition. Unlike the detailed clinical management of the neonate described by Heap J et al., the presented case emphasises the importance of genetic diagnostics and the implications for future pregnancies, including the parents' heterozygous carrier status [8].

While both cases highlight the profound impact of HI, they represent different stages of management: the male neonate's ongoing clinical care and the genetic counselling and planning for the 29-year-old female. The neonate's case illustrates the immediate and intensive therapeutic interventions required for HI, while the female's case outlines the significance of genetic testing in understanding and managing the risk of recurrence in future pregnancies [8]. In summary, these cases collectively emphasise the importance of a comprehensive approach to HI that incorporates both acute clinical management and genetic counselling. Early identification and ongoing care can significantly improve the quality of life for individuals with HI, while genetic insights provide essential information for family planning and understanding the hereditary nature of the disease.

The case of a 24-year-old pregnant woman detailed by Nikbina M and Sayahi M, in Al-Hadi Clinic, Iran, and the presented case of a 29-year-old female referred to AVBRH for genetic counselling both involve complex pregnancies complicated by HI, though with significant differences and similarities that warrant discussion [9]. In the Al-Hadi Clinic case, the 24-year-old woman, with no prior genetic testing or family history of HI, delivered a male newborn at 36 weeks and two days of gestation via caesarean section due to foetal distress [9]. The infant presented with classical signs of HI, including ichthyosis of the scalp, face, and neck, along with characteristic facial distortions such as outward-pouting lips, compressed ear pinna, and ectropion [9]. Despite Neonatal Intensive Care Unit (NICU) intervention, the newborn succumbed on the fifth day post-delivery due to complications related to the severe skin barrier defect inherent to HI [9].

Conversely, the presented case at AVBRH includes a 29-year-old female with a second-degree consanguineous marriage and a past history of an abnormal infant diagnosed postnatally with HI. The presented patient had undergone comprehensive genetic counselling and testing, which revealed a novel heterozygous deletion mutation c.6368delC (p.S2123fs*22) in exon 41 of the ABCA12 gene, confirming a diagnosis of autosomal recessive ichthyosis 4B (Harlequin) and autosomal recessive ichthyosis 4A (OMIM ID:607800). In both cases, the newborns displayed severe physical manifestations of HI shortly after birth. Despite therapeutic interventions, both newborns had poor outcomes, with one infant dying on the fifth day and the presented case resulting in a stillbirth [9]. The absence of prenatal genetic examinations in both pregnancies initially underscores the challenges of diagnosing HI before birth, highlighting the need for genetic counselling and testing, particularly in populations with consanguineous marriages.

A noteworthy distinction lies in the hereditary testing and counselling received by the woman referred to AVBRH. Unlike the initial case, where no prenatal genetic examination was conducted, the presented case included a proper genetic investigation revealing a novel change in the ABCA12 gene [9]. This information is vital for future pregnancies and family planning. The detailed genetic assessment in the presented case facilitates a broader understanding of the inheritance pattern and recurrence risk. Early identification of genetic changes can illuminate reproductive choices and guide prenatal care to manage and anticipate complications related to HI [9]. The stark results in both cases emphasise the serious nature of this hereditary disorder and the ongoing need for research and better interventions.

One case report presented by Shruthi B et al., involved a 20-year-old primigravida who was 33 weeks gestation when she delivered a baby girl with characteristics of armor-like skin, ectropion, eclabion, and small ears with closed pinnae [10]. Unfortunately, this baby could not be fully managed due to numerous challenges, including difficulties in obtaining intravenous access and other issues, and died within three days [10]. The presented case relates to a 29-year-old woman at 38 weeks of gestation with a history of neonatal death due to HI, seeking genetic counselling. The genetic test showed that both the father and mother are carriers of the ABCA12 gene mutation, confirming a high risk of HI recurrence.

The presented case of a 29-year-old female insists on receiving proactive genetic counselling and providing information about potential possibilities for further pregnancies that were not mentioned in the case described by Shruthi B et al., [10]. The choices discussed in the counselling included invasive diagnostic procedures, such as CVS or amniocentesis, if HI could be diagnosed early in the pregnancy. Other options included PGD. Furthermore, the counselling included carrier screening of other family members to enable the couple's reproductive choices within the larger family system. These interventions were designed to help the couple make informed decisions regarding future childbearing while minimising the risk of recurrence in subsequent pregnancies.

In both cases, it is apparent that consanguineous marriage was an important factor that led to autosomal recessive inheritance, which means that before planning for a family, genetic consultation and advice should be sought [10]. In relation to the case, there are similarities between both cases, especially regarding the features of HI, which is characterised by shield-shaped, hard, and scaly skin with deep clefts on the face, as well as excessive opening of the eyes and mouth and other severe physical manifestations [10]. Both patients had second-degree consanguineous marriages; the incidence of autosomal recessive disorders like HI is higher among them [10].

A comparative analysis between the case report and previously published reports has been presented in [Table/Fig-2] [7-11].

For HI, early treatment involves intensive care to manage these complications, and neonatal management consists of topical

Author's name	Place/year of the study	Patient/neonate details	Presentation of Harlequin Ichthyosis (HI)	Genetic findings	Intervention/outcome	Clinical insights
Auriti C et al., [7]	Italy/2020	Neonate born at 35 weeks via caesarean due to Premature Rupture of Membranes (PROM).	Classic signs of HI: thickened skin, keratotic scales, ectropion, eclabium, dysmorphisms.	Compound heterozygosity in the ABCA12 gene: c.4036delG and c.7444C>T variations.	Prompt dermatological and systemic management; significant improvement, with the possibility of acitretin cessation by 10 months of age.	Emphasises the importance of immediate and ongoing medical management and its effects in improving outcomes for neonates with HI.
Heap J et al., [8]	America/2020	Male neonate born to second cousins.	Classic HI features: hyperkeratotic skin, ectropion, eclabium, rudimentary pinnae, nostrils, and digit fusion.	Diagnosis was confirmed clinically; characteristic features of HI were observed in the neonate. No prior genetic testing.	Intensive postnatal care, ongoing management with acitretin, good quality of life at 12 years, but persistent dermatological and visual issues.	Emphasises the importance of postnatal care and multidisciplinary support in managing the complications of HI.
Nikbina M et al., [9]	Iran/2018	24-year-old pregnant woman with no family history of HI, gave birth at 36 weeks and 2 days due to foetal distress.	Infant exhibited classical HI features: ichthyosis of scalp, face, neck, facial distortions (outward-pouting lips, compressed ear pinna).	No prior genetic testing or family history.	Neonate succumbed on the 5th day post-delivery due to complications from HI's severe skin barrier defect.	Highlights the critical importance of early genetic testing, prenatal intervention, and genetic counselling in pregnancies at risk for HI.

Shruthi B et al., [10]	India/2016	20-year-old primigravida at 33 weeks gestation with preterm delivery.	Armor-like skin, ectropion, eclabion, small ear with closed pinnae.	Not specified in the case.	Limited management due to challenges; neonate passed away within three days.	Highlights need for timely intervention despite socioeconomic or logistic limitations.
Shrestha AB et al., [11]	India/2020	20-year-old woman with PPROM at 36 weeks; previous pregnancy complications.	Infant born with HI, but not tested prenatally; typical features of HI observed post-birth.	No prior genetic testing was done, also there was no significant family history.	Limited management due to socioeconomic factors; father refused treatment despite counselling.	Highlights the critical role of prenatal diagnosis and socioeconomic factors influencing treatment decisions in rare congenital diseases like HI.
29-year-old female (AVBRH)	India/2016	29-year-old female with second-degree consanguineous marriage and a stillborn child diagnosed with HI.	Child displayed severe physical features of HI.	Heterozygous deletion mutation c.6368delC (p.S2123fs*22) in exon 41 of ABCA12 gene, consistent with Ichthyosis autosomal recessive 4B and 4A.	Stillbirth in present case. Genetic testing was done for future pregnancies.	Early genetic diagnosis is critical for reproductive planning. The case shows the importance of genetic counselling for high-risk pregnancies and consanguineous unions.

[Table/Fig-2]: Comparison of the findings of previous studies with present study [7-11].

emollients, keratolytics, and oral retinoids such as acitretin to decrease the thickness of the skin [1,11]. Multidisciplinary support from dermatologists, neonatologists, and genetic counsellors can aid in managing the complications of HI and improve the survival rate [5,12].

Patients with HI will need follow-up dermatologic management and treatment, including skin moisturisation, surveillance, and treatment of infections or other complications [3,6]. Oral retinoids, like acitretin, can slowly ameliorate the cutaneous condition over the years. The affected families, particularly those with consanguineous marriages, would need genetic counselling to assess the likelihood of recurrence in subsequent pregnancies [2,8,11]. Options such as amniocentesis or CVS, as well as PGD in IVF, would help prevent the recurrence of HI in subsequent children [1]. This will continue to be a topic of exploration in gene therapy, including advancements such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas9) [1,3,12].

CONCLUSION(S)

The presented case demonstrates the importance of genetic counselling and prenatal diagnosis of HI in couples with consanguinity, especially in parts of the world with a high risk of autosomal recessive disorders. A novel ABCA12 gene mutation has been found, which is useful in planning future pregnancies and underscores the role of genetic sequencing. An extended response specific to genetics and screening enhancements may be beneficial in reducing the risks associated with rare genetic disorders, thereby enhancing the management of such disorders in at-risk populations in the future.

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