International Journal of Biomedicine 14(1) (2024) 182-186
http://dx.doi.org/10.21103/Article14(1)_CR7

CASE REPORT

INTERNATIONAL JOURNAL OF BIOMEDICINE

Harlequin Ichthyosis – Genetic and Dermatological Challenges: A Case Report and Literature Review

Brikene Elshani[1], Astrit M. Gashi[1*], Besa Selimi[2], Arion Elshani[2]

[1]*Department of Obstetrics and Gynecology, University Clinical Centre of Kosovo, Faculty of Medicine, University of Prishtina, Prishtina, Kosovo*
[2]*Faculty of Medicine, University of Prishtina, Prishtina, Kosovo*

Abstract

Harlequin ichthyosis (HI) is an extremely rare and severe genetic skin disorder characterized by thick, diamond-shaped scales covering the body, often giving the appearance of a harlequin costume. This paper provides an overview of the genetic and dermatological aspects of HI, delving into its etiology, clinical manifestations, and management. The genetic underpinnings of HI involve mutations in the *ABCA12* gene, leading to impaired skin barrier function and abnormal keratinization. Understanding the molecular basis of the disorder is crucial for accurate diagnosis and potential therapeutic interventions.

Clinically, HI presents challenges related to skin integrity, thermoregulation, and potential complications, such as infections. The management of HI requires a multidisciplinary approach involving dermatologists, geneticists, and other healthcare professionals. Supportive care, including emollients, careful bathing, and prevention of infections, is essential to improve the quality of life for individuals affected by this condition.

Despite its rarity and severity, advancements in medical research and genetic therapies offer hope for improved treatments and interventions. This paper aims to contribute to the collective understanding of HI, fostering ongoing research and compassionate care for those living with this unique and challenging dermatological condition. We presented a premature eutrophic harlequin baby, born at 32+ weeks of gestation via emergency C-section. A clinical diagnosis was established minutes after birth, based on the typical features of HI, from scaly skin, marked fissures, and limbs in flexion contractures to prominent eclabium and bilateral ectropion.**(International Journal of Biomedicine. 2024;14(1):182-186.)**

Keywords: Harlequin ichthyosis • ectropion • scaly skin • consanguinity • *ABCA12* gene

For citation: Elshani B, Gashi AM, Selimi B, Elshani A. Harlequin Ichthyosis – Genetic and Dermatological Challenges: A Case Report and Literature Review. International Journal of Biomedicine. 2024;14(1):182-186. doi:10.21103/Article14(1)_CR7

Introduction

Ichthyosis encompasses a large group of skin disorders that share an abnormal stratum corneum proliferation and shedding.[1-4] They are characterized by dry, rough, scaly skin from a mild to severe extent.[2,4] The word ichthyosis comes from the Greek word ichthyos – resembling fish, reflecting the cutaneous scaling pathognomonic for this disorder.[3] Despite many attempts to establish a classification through genotype-phenotype correlation and molecular basis, different terminologies for ichthyosis remain in practice worldwide.[1]

The epidermal barrier function is maintained by a regular pattern of stratum corneum differentiation, which is composed of keratinocytes (known as hydrophilic bricks) and inter-keratinocytes lipids serving as a barrier to water loss (the mortar). Specific mutations in "barrier" proteins and enzymes disrupt the lipid bilayer, hence barrier integrity, resulting in ichthyosis.[4-7]

Congenital ichthyosis manifests in a broad clinical heterogeneity and genetic profile, from autosomal recessive to dominant and recessive X-linked ichthyosis. Autosomal recessive congenital ichthyosis (ARCI) is a modified term that covers mostly non-syndrome ichthyosis: HI, lamellar ichthyosis, and congenital ichthyosiform erythroderma.[1] Newborns are

***Corresponding author**: Astrit M Gashi, Department of Obstetrics and Gynecology, University Clinical Centre of Kosovo, University of Prishtina, Prishtina, Kosovo. Email: astritgashi772@gmail.com*

encased in a collodion membrane, with a different extension of hyperkeratosis and scales.[1,2,5]

HI, also known as keratosis diffusa fetalis, ichthyosis fetalis, or harlequin fetus, is a rare, yet the most severe and escalated, type of ichthyosis.[3,5,7-9]

The pattern of inheritance is autosomal recessive. This pattern is supported by consanguinity in some families. The recurrence rate in subsequent pregnancies is 25%.[6,7,9] The *ABCA12* gene located on chromosome 2q34 encodes the ATP binding cassette transporter 12.[8,9,10-12] Mutations in this gene lead to defective lipid transport via lamellar granules in the keratinocytes, resulting in malformation of the epidermal lipid barrier and ichthyosis phenotypes. [8,9,13]

Harlequin fetuses are often born prematurely.[7,14] A newborn's skin typically presents with hard, thickened scales and yellowish-grey, diamond-shaped plaques covering most of their bodies. Plaques are separated by deep polygonal erythematous fissures that are formed prenatally. Although they transverse the whole body, scalp fissures are usually more prominent. The presence of hard plaques and fissures gives the appearance of a cracked armor coat that causes limb flexion contractures and restrictive lung movement, sometimes followed by compartment syndrome, with indistinguishable toes in some cases.[1,3,4,8,9,11-13,15]

Other clinical features associated with HI are flattened to the absent nose, dysplastic ears to varying degrees, alopecia, dysfunctional sweat glands, eclabium, and bilateral ectropion. The latter ones are caused by tightness and skin tension that forces lips and eyelids to turn inside out, exposing the mucosal lining. The O-shaped mouth of these newborns also resembles a fish's mouth.[8,12,14-16]

Newborns with HI have an extremely high mortality rate during the neonatal period. The high mortality rate explains fulminant complications associated with hyperkeratosis, such as sepsis in 75% of cases and respiratory failure in 25%, or both.[1,6,8,11,13,15] There have been reported cases of developmental delays, growth retardation, and microcephaly.[12,16,17]

A severely impaired skin barrier makes these newborns prone to excessive water loss and electrolyte imbalances with hypernatremic dehydration and hypothermia.[12,16] On the other hand, ectropion increases the risk of developing exposure to keratitis and restrictive mouth movements, inevitably requiring nasogastric tube feeding.[13]

Neonates who survive the perinatal period under intensive therapy, after a few weeks, shed the armor-like coat but, over time, develop severe ichthyosiform erythroderma.[8,11,18] In addition, extracutaneous manifestations, keratoderma, and skin infections remain for life.[15] Usually, a diagnosis is made during delivery because of the characteristic features.[13] A sonographic prenatal diagnosis is often made during the early third trimester.[14,18]

Features suggestive of HI during 3/4-D ultrasonography are bulging eyes, large open mouth, flattened nose, abnormal limbs in general, or micromelia. Other features include snowflake signs suggesting dense floating particles/plaques in amniotic fluid, poly/oligohydramnios, and intrauterine growth restriction.[9,14,18]

Molecular genetics methods via prenatal fetal DNA testing currently play an irreplaceable role in diagnoses of ichthyoses. Amniocentesis and chorionic villus sampling have replaced fetal skin biopsy as less invasive procedures.[8,9,13]

Newborns with HI require intensive multidisciplinary care. Apart from the complications caused by the infant's immature growth, actions should be taken to prevent electrolyte imbalance, respiratory distress, malnutrition, and infection, such as incubation with added humidity, respiratory support, nasogastric feeding, regular serum electrolytes, topical antibiotics, fissure cultures, daily bathing, and applying only bland emollients. Also, systemic retinoids have been shown to increase survival rates.[3,7,13,15]

Case Presentation

A 28-year-old primigravida during triage was admitted to our Clinic with obstetric pain in preterm labor at 32w+4d based on the first day of her last menstrual period. During the consultation, 7 previous ultrasound reports were evaluated. No abnormal findings were found. She had a negative consanguinity history of marriage. A non-invasive prenatal test was performed during the 10th week of gestation. The test was performed to evaluate risk for certain aneuploid and deletional syndromes, and the test results were interpreted as low risk.

On admission ultrasound, reduced amniotic fluid was noted, the baby's lie was breech, and fetal heart rate was normal. On obstetrical exam, the cervix showed 40% effacement with 4cm dilation. Membranes were intact, and soft, small tissues were palpated as the presenting part. Because of progressed dilation, one dose of 12 mg of dexamethasone was administered IM during CTG monitoring; no variable and late decelerations were noted.

Because of oligohydramnios and preterm labor in progress with the fetus in a breech position, an emergency cesarean section was performed to deliver the baby. A male, 2000 g weight, 39 cm of height, and 34 cm head circumference was born. First, the baby didn't show any signs of life, which made the specialists think of a macerated baby. The baby was in a state of suspended animation, where just about half a minute later, the baby started crying and moving. In the first minute of life, evaluated well-being by the neonatal specialists was 5 points, after the 5 minutes of life - 6 points. An immediate clinical diagnosis based on the clinical features of the newborn was made (Images 1-3). During the clinical exam, the skin was covered with thick yellow plaques in a diamond shape, separated by deep fissures that were marked in the scalp and trunk. Scalp fissures demarcated only parts covered with membrane. The hair-covered scalp was not separated by fissures in between. Flat fontanels were noted. Eyelid ectropion was more prominent than eclabium, broad nose and underdeveloped external ears attached to the scalp and covered with membrane. Limbs were fixed in flexion contractures. Fewer cracks were noted on the limbs. Toes were incurved, and palms were swollen and claw-like, with well-developed digits. Despite prematurity, the newborn was eutrophic.

The newborn was isolated in a humidified incubator, and feeding was maintained with a nasogastric tube. The first

few hours, body temp was 35°C, respiratory rate - 53, heart rate - 155 bpm, and SpO2 - 96%. The abdomen sonography showed no abnormalities during examination, and the heart echocardiogram showed neither. Despite the vigorous multidisciplinary management after the first 3 hours, clinical deterioration with costal retractions was noted. The newborn expired after 12 hours, with the cause of death being acute respiratory distress syndrome.

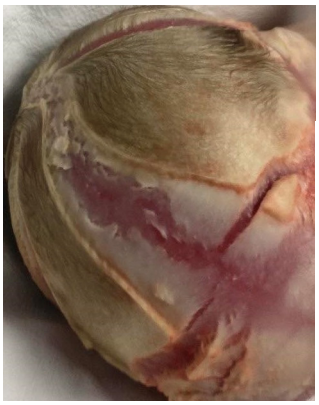

Image 1. *Marked fissures on the scalp.*

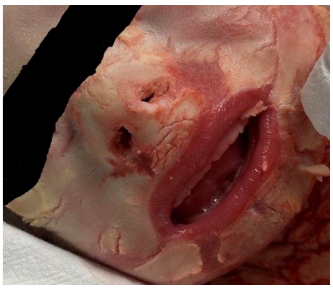

Image 2. *Flattened broad nose, prominent ectropion, and eclabium.*

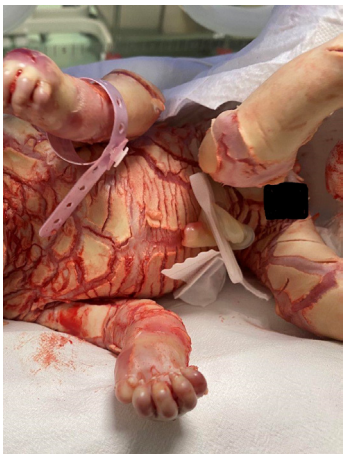

Image 3. *Severe extension of diamond-shaped hard plaques separated by deep fissures, prominent in the upper trunk region.*

Discussion

Ichthyosis represents a wide heterogeneous group of inherited and acquired skin disorders. The most severe form of congenital ichthyosis is HI, a Mendelian disorder of cornification, generally with an autosomal recessive pattern of inheritance.[19] The first case of HI was described in 1750 by Oliver Heart, while first prenatally diagnosed in 1982. Currently, its incidence is 1:300.000 cases. No evidence of frequency regarding sex, race, or ethnicity distribution was found.[13,14] Its rare manifestation shows the importance of family history during evaluation in establishing the pattern of inheritance. A positive history of parental consanguinity suggests a recessive pattern, while an affected parent and a sibling would point toward autosomal dominant inheritance.[4] In our case, no previously affected family members were found during pedigree evaluation, and a negative parental consanguinity was confirmed.

Liang et al. exhibited a rare phenomenon of confirmed prenatal diagnosis of HI after a previous birth of a fetus with HI. Rathore et al. presented a HI case with a second-degree consanguineous marriage.[9,20] Habib et al.[7] presented a case of a "harlequin fetus" from a consanguineous couple, but contrary to the case mentioned above, their relatives had a similar baby years ago. Suzumori and Kanzaki[21] described a case with 3 consecutive harlequin fetuses confirmed via fetal skin biopsy with a negative history of consanguinity, suggesting the autosomal dominant trait of inheritance.

HI is presented with very typical clinical-pathological features. Dry, scaly plaques in a diamond shape, separated by deep fissures from which the origin of its name arises like a traditional harlequin's costume and a characteristic face pulled wide open resembling a harlequin's smile.[8,16] We presented a premature eutrophic harlequin fetus, born at 32+ weeks of gestation via emergency C-section. An event of suspended animation was described; the fetus was thought by the surgeons to be a dead macerated fetus, for a few seconds. Jilmudi also described the state of suspended animation and its incidence, though it still has not been reported in the available literature.[22] A clinical diagnosis was established minutes after birth, based on the typical features of HI, from scaly skin, marked fissures, and limbs in flexion contractures to prominent eclabium and bilateral ectropion. Hepatomegaly, collapsed bowel, and prominent gall bladder were reported during the evaluation of this patient.[18] Our case showed no abnormal findings on abdominal sonography.

On postmortem examinations of harlequin fetuses, lung and liver fibrosis and ileum infarction have been described. Brain autopsies of maldevelopment with ischemic-necrotic lesions have been observed, such as severe cholestasis and enlarged thymus. Also, microcephaly, growth retardation, and developmental delay have been reported.[18,22] Baldo et al.[12] reported a rare case with an early onset of juvenile idiopathic arthritis in a 7-year-old boy with HI, suggesting that polyarthritis also could be a unique manifestation of HI. These findings allow space for further research to provide evidence on whether these lesions and manifestations are a result of the initial injury or that this disease is more intricate, involving other tissues in addition to the skin. Prenatal diagnosis and genetic counseling should be offered to all couples with previously affected babies.[9,13] The gold standard diagnostic prenatal test for HI is fetal DNA direct sequence analysis of the *ABCA12* gene, derived from amniotic fluid cells at 16 weeks of gestation.[7,16]

Immune-histological studies of skin have revealed that the focal structure where the HI phenotype begins is the hair canal keratinization at 17 weeks of gestation, subsequently from 20 weeks in the entire hairy skin.[14,18,23] Years ago, prenatal diagnosis of HI relied on fetal skin biopsy. Taken from fetuses around 21-23 weeks of gestation, when abnormal skin was thought to be expressed in the entire body surface.[23]

Electron microscopy may identify atypical intraepidermal vesicles by 16 weeks of gestation; light microscopy can show premature keratinization by the 20th to 22nd week,[7] while amniocentesis could show aggregated lipidic vesicles in keratinocytes by the 17th week of gestation.

Its rare congenital nature makes sonographic early prenatal diagnosis challenging, especially without known risk factors and because of mid-gestation phenotype development. Hence, a prenatal sonographic diagnosis could be implemented by the second trimester.[14,18]

In our study, a diagnosis was established after birth based on the clinical features. A prenatal genetic test conducted during early pregnancy for certain aneuploidies and deletional syndromes resulted in a negative conclusion, and on ultrasound, no abnormal features during pregnancy were detected. On admission, a breech-presented fetus with oligohydramnios was described.

The most common findings on ¾ dimensional ultrasound during pregnancy are ectropion, eclabium, flat nose, short limbs, swollen hands and feet, abnormal position, intrauterine growth restriction, and polyhydramnios. Less often, breech presentation, oligohydramnios, and abnormal fetal movements.[3,13,18]

In a study by Liang et al., karyotype analysis of the amniotic fluid at 20 weeks of gestation resulted in no chromosomal abnormalities, while sonography at 24 weeks of gestation showed thickened soft tissue in the anterior region of the eyeballs.[20] In a study by Rathore, a 3/4-dimensional sonographic diagnosis was established only after a confirmed HI previous pregnancy. At 26 weeks of gestation, the diagnosis was based on sonographic markers like ectropion, eclabium, short foot length, incurved toes, and polyhydramnios.[9] In Berg et al.,[18] although features of HI were encountered on ultrasound during pregnancy, they still couldn't diagnose the condition until labor, at 35 weeks of gestation, because of premature rupture of membranes. Sepsis and respiratory failure are the most common causes of death. Because of thickened skin, chest wall movements get restricted, making breathing a painful mechanism that results in poor pulmonary ventilation. The development of respiratory failure is attributed to aspiration of amniotic fluid with thick skin particles.[24]

The mortality of patients with HI is still high around the world. Most of them die in the first few hours to days of life due to secondary complications, such as infection, dehydration, and respiratory insufficiency. Many factors contribute to the survival of these patients. It has been reported that fetuses with a heterozygote mutation had a higher survival rate than those with a homozygous gene function loss. Also, milder phenotypes have been described among individuals with missense mutations of the *ABCA12* gene, in comparison to nonsense mutations.[4,6,17] In a study by Rajpopat,[24] where 45 patients participated, the survivors' ages ranged from 10 months to 25 years, and the overall survival rate was 56%. A retrospective study by Shibata et al. [25] during the 2005-2010 period concluded that early intubation can improve outcomes for harlequin fetuses due to the development of respiratory insufficiency. Also, systemic retinoids, early antibiotic administration, and intensive care units have all improved patient survival rates.[25] Rajpopat et al.[24] showed the effects of systemic retinoids. In the retinoid-treated group, 83% of patients survived, compared to the 76% mortality rate from the untreated group.

Conclusion

HI is a rare, severe chronic disorder of cornification with a poor prognosis during the neonatal period. Early life complications, such as sepsis, dehydration, and respiratory failure, can occur. Over the decades, many synonyms have been given to this skin condition, all of them resembling the phenotypical features of these babies. Usually, a diagnosis is made based on clinical appearance during delivery. Risk factors contributing to early prenatal diagnosis are positive family history, previous pregnancies with similar phenotypes, and family consanguinity. Second-trimester sonographic markers can lead to a prenatal diagnosis, especially after a previously confirmed pregnancy with HI. The typical facial features, reduced fetal movements, intrauterine growth restriction, and amniotic fluid changes are the most encountered changes during sonographic evaluation. These babies are usually born prematurely; suspended animation is a possible event during labor. Other tissues involved have been described. In addition to the skin changes, neurodevelopment delays have also been noted. Systemic retinoids and multidisciplinary immediate management have been shown to improve outcomes and increase survival rates.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

We are grateful to Dr. Faton Krasniqi for the critical evaluation and final approval of the manuscript.

Ethical Considerations

The institutional ethical board has approved this research with registration number 3430. The patient provided written informed consent to publish case-associated data and accompanying images.

References

1. Oji V, Tadini G, Akiyama M, Blanchet Bardon C, Bodemer C, Bourrat E, Coudiere P, DiGiovanna JJ, Elias P, Fischer J, Fleckman P, Gina M, Harper J, Hashimoto T, Hausser I, Hennies HC, Hohl D, Hovnanian A, Ishida-Yamamoto A, Jacyk WK, Leachman S, Leigh I, Mazereeuw-Hautier J, Milstone L, Morice-Picard F, Paller AS, Richard G, Schmuth M, Shimizu H, Sprecher E, Van Steensel M, Taïeb A, Toro JR, Vabres P, Vahlquist A, Williams M, Traupe H. Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Sorèze 2009.

J Am Acad Dermatol. 2010 Oct;63(4):607-41. doi: 10.1016/j.jaad.2009.11.020. PMID: 20643494.
2. Fischer J. Autosomal recessive congenital ichthyosis. J Invest Dermatol. 2009 Jun;129(6):1319-21. doi: 10.1038/jid.2009.57. PMID: 19434086.
3. Craiglow BG. Ichthyosis in the newborn. Semin Perinatol. 2013 Feb;37(1):26-31. doi: 10.1053/j.semperi.2012.11.001. PMID: 23419760; PMCID: PMC3758581.
4. DiGiovanna JJ, Robinson-Bostom L. Ichthyosis: etiology, diagnosis, and management. Am J Clin Dermatol. 2003;4(2):81-95. doi: 10.2165/00128071-200304020-00002. PMID: 12553849.
5. Cuperus E, Bygum A, Boeckmann L, Bodemer C, Bolling MC, Caproni M, Diociaiuti A, Emmert S, Fischer J, Gostynski A, Guez S, van Gijn ME, Hannulla-Jouppi K, Has C, Hernández-Martín A, Martinez AE, Mazereeuw-Hautier J, Medvecz M, Neri I, Sigurdsson V, Suessmuth K, Traupe H, Oji V, Pasmans SGMA. Proposal for a 6-step approach for differential diagnosis of neonatal erythroderma. J Eur Acad Dermatol Venereol. 2022 Jul;36(7):973-986. doi: 10.1111/jdv.18043. Epub 2022 Mar 15. PMID: 35238435; PMCID: PMC9310754.
6. Marukian NV, Choate KA. Recent advances in understanding ichthyosis pathogenesis. F1000Res. 2016 Jun 24;5:F1000 Faculty Rev-1497. doi: 10.12688/f1000research.8584.1. PMID: 27408699; PMCID: PMC4926734.
7. Habib A, Pasha W, Raza N, Hameed A. Harlequin ichthyosis in two siblings. J Coll Physicians Surg Pak. 2011 Aug;21(8):503-5. PMID: 21798141.
8. Pinkova B, Buckova H, Borska R, Fajkusova L. Types of congenital nonsyndromic ichthyoses. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2020 Dec;164(4):357-365. doi: 10.5507/bp.2020.050. Epub 2020 Oct 21. PMID: 33087941.
9. Rathore S, David LS, Beck MM, Bindra MS, Arunachal G. Harlequin Ichthyosis: Prenatal Diagnosis of a Rare Yet Severe Genetic Dermatosis. J Clin Diagn Res. 2015 Nov;9(11):QD04-6. doi: 10.7860/JCDR/2015/15250.6705. Epub 2015 Nov 1. PMID: 26675324; PMCID: PMC4668483.
10. Vega Almendra N, Aranibar Duran L. Ictiosis hereditaria: desafío diagnóstico y terapéutico [Hereditary ichthyosis: A diagnostic and therapeutic challenge]. Rev Chil Pediatr. 2016 May-Jun;87(3):213-23. Spanish. doi: 10.1016/j.rchipe.2015.07.025. Epub 2015 Oct 23. PMID: 26471314.
11. Elias PM, Williams ML, Holleran WM, Jiang YJ, Schmuth M. Pathogenesis of permeability barrier abnormalities in the ichthyoses: inherited disorders of lipid metabolism. J Lipid Res. 2008 Apr;49(4):697-714. doi: 10.1194/jlr.R800002-JLR200. Epub 2008 Feb 2. PMID: 18245815; PMCID: PMC2844331.
12. Baldo F, Brena M, Carbogno S, Minoia F, Lanni S, Guez S, Petaccia A, Agostoni C, Cimaz R, Filocamo G. Juvenile idiopathic arthritis in Harlequin ichthyosis, a rare combination or the clinical spectrum of the disease? Report of a child treated with etanercept and review of the literature. Pediatr Rheumatol Online J. 2021 Jun 3;19(1):80. doi: 10.1186/s12969-021-00571-9. Erratum in: Pediatr Rheumatol Online J. 2021 Jul 23;19(1):115. PMID: 34082764; PMCID: PMC8173856.
13. Elkhatib AM, Omar M. Ichthyosis Fetalis. 2023 Aug 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 32809327.
14. Vijayakumari M, Reddy DK, Routhu M, Vuchuru M, Reddy NS. Prenatal diagnosis of harlequin ichthyosis: a case report. Obstet Gynecol Sci. 2020 Jan;63(1):94-97. doi: 10.5468/ogs.2020.63.1.94. Epub 2019 Dec 9. PMID: 31970133; PMCID: PMC6962590.
15. Kün-Darbois JD, Molin A, Jeanne-Pasquier C, Paré A, Bénateau H, Veyssière A. Facial features in Harlequin ichthyosis: Clinical findings about 4 cases. Rev Stomatol Chir Maxillofac Chir Orale. 2016 Feb;117(1):51-3. doi: 10.1016/j.revsto.2015.11.007. Epub 2015 Dec 28. PMID: 26740202.
16. Shrestha AB, Biswas P, Shrestha S, Riyaz R, Nawaz MH, Shrestha S, Hossainy L. Harlequin ichthyosis: A case report and literature review. Clin Case Rep. 2022 Dec 5;10(12):e6709. doi: 10.1002/ccr3.6709. PMID: 36483862; PMCID: PMC9723482.
17. Salehin S, Azizimoghadam A, Abdollahimohammad A, Babaeipour-Divshali M. Harlequin ichthyosis: Case report. J Res Med Sci. 2013 Nov;18(11):1004-5. PMID: 24520234; PMCID: PMC3906774.
18. Berg C, Geipel A, Kohl M, Krokowski M, Baschat AA, Germer U, Gembruch U. Prenatal sonographic features of Harlequin ichthyosis. Arch Gynecol Obstet. 2003 Apr;268(1):48-51. doi: 10.1007/s00404-002-0333-4. Epub 2002 Jul 6. PMID: 12673476.
19. Schmuth M, Martinz V, Janecke AR, Fauth C, Schossig A, Zschocke J, Gruber R. Inherited ichthyoses/generalized Mendelian disorders of cornification. Eur J Hum Genet. 2013 Feb;21(2):123-33. doi: 10.1038/ejhg.2012.121. Epub 2012 Jun 27. PMID: 22739337; PMCID: PMC3548255.
20. Liang Q, Xiong F, Liang X, Zheng D, Su S, Wen Y, Wang X. Two successive cases of fetal harlequin ichthyosis: A case report. Exp Ther Med. 2019 Jan;17(1):449-452. doi: 10.3892/etm.2018.6917. Epub 2018 Nov 2. PMID: 30651820; PMCID: PMC6307384.
21. Suzumori K, Kanzaki T. Prenatal diagnosis of harlequin ichthyosis by fetal skin biopsy; report of two cases. Prenat Diagn. 1991 Jul;11(7):451-7. doi: 10.1002/pd.1970110707. PMID: 1754561.
22. Jilumudi UB. Harlequin ichthyosis: A medico legal case report & review of literature with peculiar findings in autopsy. J Forensic Leg Med. 2012 Aug;19(6):352-4. doi: 10.1016/j.jflm.2012.02.019. Epub 2012 Mar 7. PMID: 22847055.
23. Akiyama M. The pathogenesis of severe congenital ichthyosis of the neonate. J Dermatol Sci. 1999 Sep;21(2):96-104. doi: 10.1016/s0923-1811(99)00024-9. PMID: 10511478.
24. Rajpopat S, Moss C, Mellerio J, Vahlquist A, Gånemo A, Hellstrom-Pigg M, Ilchyshyn A, Burrows N, Lestringant G, Taylor A, Kennedy C, Paige D, Harper J, Glover M, Fleckman P, Everman D, Fouani M, Kayserili H, Purvis D, Hobson E, Chu C, Mein C, Kelsell D, O'Toole E. Harlequin ichthyosis: a review of clinical and molecular findings in 45 cases. Arch Dermatol. 2011 Jun;147(6):681-6. doi: 10.1001/archdermatol.2011.9. Epub 2011 Feb 21. PMID: 21339420.
25. Shibata A, Akiyama M. Epidemiology, medical genetics, diagnosis and treatment of harlequin ichthyosis in Japan. Pediatr Int. 2015 Aug;57(4):516-22. doi: 10.1111/ped.12638.