Case Report

J Genet Med 2019;16(2):62-66
https://doi.org/10.5734/JGM.2019.16.2.62
ISSN 1226-1769 (Print) 2383-8442 (Online)

JGM Journal of Genetic Medicine

A newborn girl with harlequin ichthyosis genetically confirmed by *ABCA12* analysis

Jihye Kim, Jung Min Ko*, Seung Han Shin, Ee-Kyung Kim, and Han-Suk Kim
Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, Seoul, Korea

Harlequin ichthyosis (HI, OMIM #242500) is one of the most severe skin diseases among the autosomal recessive congenital ichthyoses, with high morbidity and mortality, particularly in newborns. Clinically, it is characterized by a typical appearance of generalized, thick, yellowish, hyperkeratotic plates with deep erythematous fissures on the skin. Herein, we present the case of a newborn girl with HI that was genetically confirmed by targeted gene panel analysis. The premature baby was encased in an opaque white membrane with erosion covering the skin of the entire body except the lips, with her hands and feet restricted by the membrane. Humidification, emollient, and retinoic acid treatment were started; the thick ichthyosis gradually peeled off and the underlying skin was only covered with thin scales. Targeted gene panel analysis using next-generation sequencing and validation with Sanger sequencing and quantitative polymerase chain reaction analyses confirmed compound heterozygous mutations of the *ABCA12* gene (p.N1380S and a partial gene deletion encompassing exon 9). The parents were carriers for each of the identified mutations. Early recognition of the genetic etiology of congenital ichthyosis can, thus, facilitate genetic counseling for patients and their families.

Key words: Ichthylsis, lamellar, Harlequin Ichthyosis, ABCA12, Autosomal recessive, Compound heterozygote.

Introduction

Ichthyoses comprise a group of genetically determined skin diseases with abnormal keratinization, resulting in thickening of the stratum corneum, xerosis, or scaling involving the skin of the entire body [1]. Harlequin ichthyosis (HI) is the most severe subtype of the autosomal recessive congenital ichthyoses (ARCI), showing a typical appearance of the so-called "collodion baby," being encased in an armor-like membrane at birth [2]. The whole-body skin of the patient has a thick and shiny plate covering, and the face and extremities show malformations, such as ectropion, eclabium, flattened ear and nose, and syndactyly or contracture of the fingers and toes.

HI is reportedly an extremely rare disease with an incidence of 1 in 3,000,000 live births [2]. Although regarded as a fatal disease in the past, gentle supportive care in the neonatal intensive care unit (NICU) and retinoic acid therapy have recently been reported to improve patient survival [2]. However, additional multidisciplinary treatment is important for managing the various deformities and complications associated with HI.

The only known causative gene for HI is *ABCA12*, which encodes the adenosine triphosphate-binding cassette transporter protein that is involved in lipid transportation to form the extracellular lipid layer in the skin. Impairment of this transport

Received: 7 May 2019, Revised: 31 July 2019, Accepted: 31 July 2019, Published: 31 December 2019
*Corresponding author: Jung Min Ko, M.D., Ph.D. https://orcid.org/0000-0002-0407-7828
Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Tel: +82-2-2072-3570, Fax: +82-2-2072-3571, E-mail: jmko@snu.ac.kr
Conflict of interest: The authors declare that they do not have any conflicts of interest.

function can diminish skin barrier permeability, resulting in poor keratinocyte differentiation and decreased desquamation [3].

Herein, we report the case of a newborn girl with genetically confirmed HI, presenting with the typical skin manifestations of the disease. The patient was treated with retinoic acid, a topical emollient, and supportive care (i.e., humidification and surgical intervention to prevent ischemic necrosis of the toes). There have been only 8 cases of HI reported in Korea to date, but all of them were diagnosed based on their clinical features and skin biopsy, without molecular genetic confirmation [4-9]. This is the first report of a Korean infant with genetically confirmed HI, who was successfully treated during the neonatal period.

Case

The girl was born via vaginal delivery at the 35 weeks and 4th day of gestation owing to maternal preterm labor and progression of cervix dilatation. Her birth height and weight were 45.5 cm (50-90th percentile) and 2,340 g (10-50th percentile), respectively. Based on the prenatal examinations, bilateral clubfeet and club hands were suspected, but no other anatomic abnormality was noted. Upon delivery, her whole-body skin was covered with an opaque white membrane with erosion. In particular, except for the lips, her entire face and ears were covered with a milk-like thick skin patch. Ectropion was observed in both eyes, but eclabium was not observed (Fig. 1A). Both hands and feet were encased by a thick membrane that looked like white bullae, with a slight tear on the heels and palms. Partial syndactyly of the right hand and right foot was obvious.

Immediately after birth, she was transferred to an incubator with the humidity set at 70% to prevent excessive water loss through the skin. No respiratory support was needed. Because the thick and opaque membrane-covered skin hindered assessment of the peripheral vein, a central umbilical vein catheter was inserted for fluid therapy and antibiotic administration. In conjunction with parenteral nutrition, enteral feeding via a nasogastric tube was started because her sucking was poor. For 10 days after birth, we advanced the total milk intake up to 130 mL/kg/day, and her body weight decreased during this time. About 11% weight loss was estimated, excluding the dressing weight at the surgical site. Since then, the weight gain was found to increase by 10 to 40 g per day with an increase in total feeding of up to 200 mL/kg/day during hospitalization. The membrane covering the skin dried and turned scaly, but there was no evidence of dehydration, such as electrolyte imbalance, an increase in hematocrit, or oliguria. On the 6th day after birth, we removed the nasogastric tube as she showed improved oral intake with the bottle. Empirical antibiotic therapy with ampicillin and gentamicin was started to prevent skin infection and neonatal sepsis. Congenital ichthyosis, epidermolytic hyperkeratosis, and Netherton syndrome were considered as differential diagnoses based on the gross dermatologic findings. We started oral retinoic acid

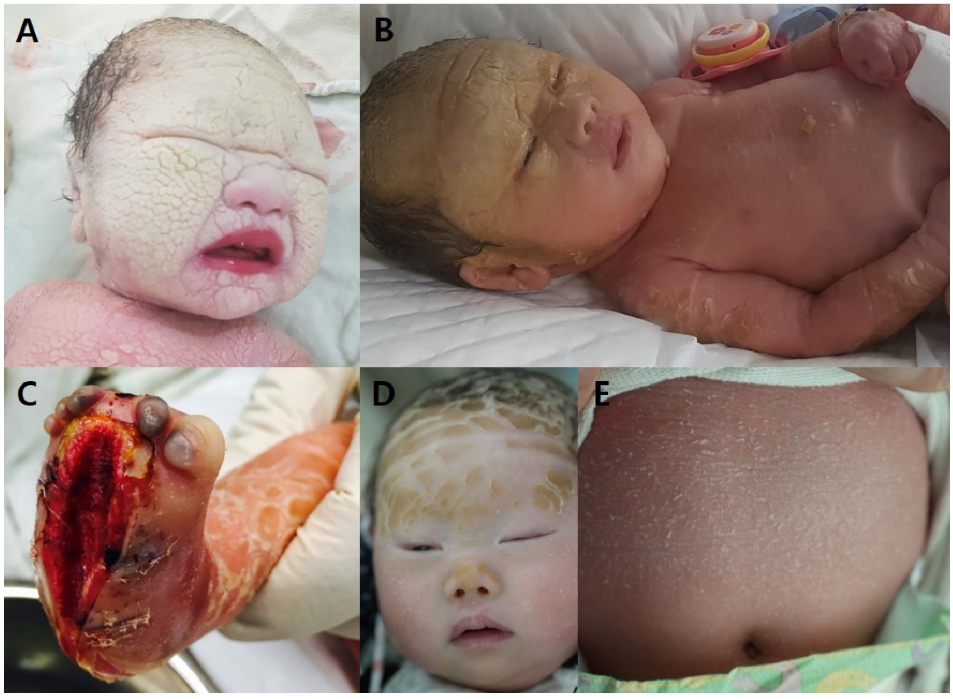

Fig. 1. Skin manifestations and the clinical course observed in our harlequin ichthyosis patient. (A) An opaque white membrane with erosion over the whole-body skin except over the lips, was noted on the first day. (B) A linear incision of fasciotomy was performed on the right sole for ischemic change in the right toes on the 4th day after birth. (C) The capsule-like membranes had peeled off and only a scale-like membrane covered the body at the 13th day after birth. (D, E) Her skin had improved around 4 months of age, and the membrane that had been covering her skin changed into a thin-scaled hyperkeratosis.

(acitretin, 1 mg/kg/day) treatment for managing the congenital ichthyosis. Petroleum jelly was applied as a moisture insulator to the whole-body skin.

On the 4th day after birth, her right toes turned dark brown as a result of reduced blood circulation due to contraction of the ichthyosis membrane. Emergent capsulotomy of the right sole was performed to relieve ischemia, after which toe color was recovered (Fig. 1B). The ichthyosis covering the whole body gradually peeled off, and approximately 20% of the membrane remained at two weeks after birth. A thin scaling was finally remained, and her ectropion had improved. The capsule-like bullae on the left toes and both hands also detracted without surgical intervention (Fig. 1C). The patient was discharged on the 27th day after birth with maintenance of skin moisturizer and emollient application. We thus planned a surgery for partial syndactyly release.

To examine the internal organ anomalies, we performed echocardiography and an ultrasonogram of the brain and abdomen. There were no abnormal findings other than a patent foramen ovale. There was no ectropion, exposure keratopathy, or lagophthalmos found upon ophthalmologic examination. She showed some limitation of movement in her limbs, which improved to some extent as the stiff membrane detached itself.

Targeted gene panel analysis for congenital ichthyosis was performed using next-generation sequencing, and the results showed one pathogenic variant on exon 28 of *ABCA12*, c.4139A>G (p.N1380S) (ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/). We additionally applied a copy number variation detection algorithm that identified a partial gene deletion encompassing exon 9 of *ABCA12*. For validation and confirmation of the two variants found, we also performed parental screening and quantitative polymerase chain reaction analysis. The mother harbored c.4139A>G (p.N1380S), and the father carried the partial gene deletion encompassing exon 9. The patient was, thus, genetically confirmed as having HI with compound heterozygous mutations of the *ABCA12* gene (Fig. 2). She took oral retinoic acid at an outpatient clinic for up to 2 months of age and had no side effects, such as an increase in liver enzymes. No aggravation of skin lesions was observed even after discontinuation of retinoic acid during 12 months of follow up (Fig. 1D, E). The patient also had no skin infection. She began eating baby food at six months of age and was easily consuming breast milk and powdered milk formula. She has been growing by a 10th to 50th percentile of body weight and a 3rd percentile of height according to the 2017 Korean National Growth Chart for children and adolescents. By the time she was 9 months old, she was able to roll over to both sides and sit without support. At the last follow-up, she was 12 months old and could walk with support.

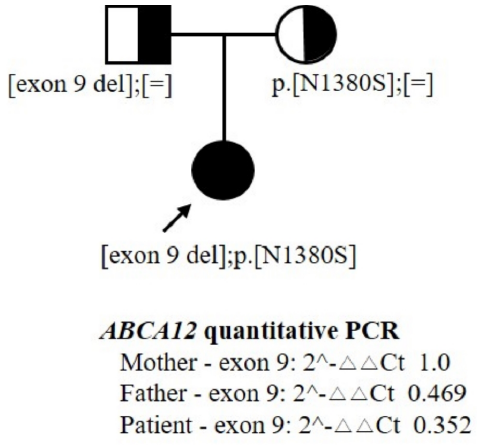

Fig. 2. The family pedigree of our patient with harlequin ichthyosis carrying recessively inherited *ABCA12* variants. The *ABCA12* alleles are represented by "[=]" (wild-type) and "c.4139A>G (p.N1380S)." A partial deletion encompassing exon 9 and a missense mutation, found by targeted gene panel analysis were validated by quantitative polymerase chain reaction (PCR) and Sanger sequencing, respectively.

Discussion

HI is the most severe subtype of ARCI congenital ichthyosis, the other subtypes of which include lamellar ichthyosis and congenital ichthyosiform erythroderma. Patients with HI show severe collodion membranes on the whole-body skin at birth, which change to erythema and scales after adaptation to the environment outside the uterus [3]. Facial deformations, such as severe ectropion, eclabium, and flattening of the ears and nose are also common clinical features. Additionally, changes to the extremities, including palmoplantar synechiae and circumferential bands of extremities, may also occur.

In 2011, Rajpopat et al. [10] reviewed 45 cases of HI and reported a mortality rate of 44% (20 of 45 cases); the main reasons for death were sepsis and respiratory failure, and the age of death was less than two months. Careful supportive care at the NICU is, thus, crucial because patients with HI experience higher transepidermal water loss compared to healthy babies, resulting in electrolyte imbalance, dehydration, and poor thermoregulation, as well as respiratory difficulty, with possible early mortality [2]. In this case, the patient had a high weight loss of 11% in the early postnatal period and required high fluid intake of 200 mL/kg/day for proper growth, which is greater than what is normally required for a baby. Fortunately, the patient did not have any problems regarding dehydration or body temperature. Although many cases of HI are preterm babies, this patient was born near

term. This might be the reason why critical clinical features, such as respiration and serum electrolyte levels, were mild.

Retinoic acid, a natural and synthetic derivative of vitamin A, is known to be an effective treatment for ichthyosiform disorders [1]. Retinoic acid is known as a ligand that combines with retinoic acid receptors and acts as a transcription factor in the nucleus [1]. Although the exact mechanism by which retinoic acid operates in the keratinocytes of patients is unknown, we can assume its effects to include the thinning of the stratum corneum, aiding of desquamation, and anti-inflammatory effects [1]. In a previous study, oral retinoic acid treatment within the first 7 days of birth was reported as being beneficial for ameliorating skin symptoms and improving survival [2]. A higher survival rate was also noted when retinoic acid was applied (83% for the retinoic acid-treated group vs. 24% for the control group) [10]. The usual dose of retinoic acid is 0.5 to 2.5 mg/kg, but this dose must be adjusted according to the patient's response. Some patients show a dramatic effect to retinoic acid, whereas only minor effects are observed in some patients [1]. Since the severity of skin lesions is reduced compared to that seen immediately after birth, the use of the medication can be discontinued; over a period of 6 months [2];however, some patients need several years to recover or have to restart treatment after discontinuation (reported in 20% of patients) [1]. To monitor side effects of retinoic acid during long-term use, regular blood tests including transaminase levels and lipid levels, and surveillance for hyperostosis are required [1].

As shown in this case, some patients with HI undergo ischemic necrosis, compartment syndrome, and auto-amputation of the limbs, due to which surgical release from constrictive plaques is often needed [3,11]. Linear incision on the palm side including constrictive bands was performed on our patient, after which the necrotic changes of the toes were reversed.

Fetal ultrasonography of our patient showed bilateral clubfeet and club hands, which seemed to be a misinterpretation of the fixed flexion and thick skin covering the hands and feet that are presented in HI [12]. For more severe cases, ectropion, an absent nose, a large gaping open mouth, and swollen or abnormal position of the hands and feet could be observed by fetal ultrasonography [13]. Amniotic fluid containing excessive skin debris could be an additional prenatal finding of this disease [13,14]. A recently published article presented 10 genetically confirmed cases of HI with prenatal sonographic features. Although eclabium, ectropion, and a flat nose were observed in more than half of the cases, the clubfeet sheen in our case were observed in only 3 of 10 cases [14]. These sonographic findings are noticeable after the mid-trimester, and are variable among patients [14]; therefore, the utility of fetal sonographic examination for prenatal detection of HI is thought to be limited.

Mutations in *TGM1*, *ABCA12*, *NIPAL4*, *CYP4F22*, *ALOX12B*, or *ALOXE3* are known to be the cause of ARCI, and mutation of *ABCA12* on chromosome 2q35 is known as the only cause of HI, the most severe subtype of ARCI [15]. Ever since *ABCA12* was first identified as the causative gene for HI in 2003 [16], approximately 100 kinds of mutations and several cases with mutations have been reported (http://www.hgmd.cf.ac.uk). ABCA12 belongs to a large superfamily of ATP-binding cassette (ABC) transporters and is expressed in epidermal keratinocytes that transport lipids to the apical surface [15]. Deletion of exon 9 is a novel mutation, even though p.N1380S has been repeatedly reported in homozygous forms in patients from Morocco and Algeria [16]. Patients with p.N1380S showed the clinical manifestation of lamellar ichthyoses, such as collodion babies, at birth, moderate to severe ichthyosis, and palmoplantar keratoderma [17,18]. In our patient, deformities of the extremities were more severe than those observed in previously reported cases with the same mutation [17,18]. The partial deletion of the gene on the counter allele may result in more severe manifestations, as those observed in our patient.

Congenital hypothyroidism is known to be a common complication in patients with HI. In a previous study on 42 collodion babies, the prevalence of congenital hypothyroidism was higher in the patient group than in the control group previously matched in terms of gestational age and birth weight (23% vs. 4%, P=0.01) [19]. The reason for the prevalence of elevated congenital hypothyroidism in HI has not been elucidated yet. However, monitoring thyroid function is needed for the early detection and proper management of thyroid dysfunction in HI [19]. In this case, thyroid stimulating hormone (TSH) was determined to be high (19.03 μIU/mL) at 3 weeks after birth, with normal thyroxine levels. TSH was normalized by 3 months of age.

Some developmental delay (causing the requirement of appropriate support for attending a school or higher education) is frequently observed, and growth problems are also common in cases of HI [10,20]. The rate of premature birth was reported to be as high as 29%, and the rate of "small for gestational age" was also high (at 40%). This suggests that fetal growth within the uterus is limited [19]. Furthermore, 2 of 10 patients with HI had malabsorption or nutritional problems in a previous study [20]. Increased hematocrit or hypernatremia has been consistently noted in all HI-affected grown-up patients, who generally have a short stature; water loss through the skin in early infancy

could contribute to growth failure, along with prenatal and nutritional problems [20]. Fortunately, our patient was born with a weight in the 10th to 50th percentile and is growing by a 10th to50th percentile of this weight after receiving NICU care.

In conclusion, we report the first case of HI with a deletion in exon 9 of the *ABCA12* gene. This is the first case of HI reported in Korea to be identified with *ABCA12* mutations. Confirmation of the causative mutations is important in genetic counseling to reduce the risk of recurrence with the help of prenatal diagnosis using fetal samples during early pregnancy [15]. Fortunately, through gentle NICU care and proper surgical treatment, the patient has grown well without serious complications to date. Since the long-term sequelae of HI are not well clarified due to the rarity of the disease, long term monitoring of individual patients' health conditions, including growth and development, is essential to identify and predict long-term prognosis of HI.

References

1. Digiovanna JJ, Mauro T, Milstone LM, Schmuth M, Toro JR. Systemic retinoids in the management of ichthyoses and related skin types. Dermatol Ther 2013;26:26-38.
2. Glick JB, Craiglow BG, Choate KA, Kato H, Fleming RE, Siegfried E, et al. Improved management of Harlequin ichthyosis with advances in neonatal intensive care. Pediatrics 2017;139:e20161003.
3. Scott CA, Rajpopat S, Di WL. Harlequin ichthyosis: ABCA12 mutations underlie defective lipid transport, reduced protease regulation and skin-barrier dysfunction. Cell Tissue Res 2013;351:281-8.
4. Ahn SJ, Hong JW. Surgical treatment of syndactyly of Harlequin ichthyosis. Arch Hand Microsurg 2018;23:184-9.
5. Choi SK, Lee HS, Oh SJ, Hwang SJ, Park IY, Kim CJ, et al. A case of Harlequin ichthyosis. Korean J Perinatol 2005;16:266-9.
6. Kim EJ, Kim S, Ma SH. A case of Harlequin ichthyosis. Korean J Perinatol 2002;13:181-4.
7. Seo SH, Chang YP, Ko KS. A case of Harlequin baby. J Korean Soc Neonatol 1997;4:97-100.
8. Lee JB, Lee SH, Lee SN, Kim CS. Electronmicroscopic study of Collodion baby. Korean J Dermatol 1981;19:93-9.
9. Cha SH, Park SD, Oh YK, Kang IK, Choi KC. Two cases of Collodion baby. Korean J Dermatol 1997;35:129-34.
10. Rajpopat S, Moss C, Mellerio J, Vahlquist A, Gånemo A, Hellstrom-Pigg M, et al. Harlequin ichthyosis: a review of clinical and molecular findings in 45 cases. Arch Dermatol 2011;147:681-6.
11. Pet MA, Gupta D, Tse RW. Harlequin ichthyosis: a surgical perspective. Pediatr Dermatol 2016;33:e327-32.
12. Liang Q, Xiong F, Liang X, Zheng D, Su S, Wen Y, et al. Two successive cases of fetal Harlequin ichthyosis: a case report. Exp Ther Med 2019;17:449-52.
13. Berg C, Geipel A, Kohl M, Krokowski M, Baschat AA, Germer U, et al. Prenatal sonographic features of Harlequin ichthyosis. Arch Gynecol Obstet 2003;268:48-51.
14. Brandão P, Seco S, Loureiro T, Ramalho C. Prenatal sonographic diagnosis of Harlequin ichthyosis. J Clin Ultrasound 2019;47:228-31.
15. Akiyama M. ABCA12 mutations and autosomal recessive congenital ichthyosis: a review of genotype/phenotype correlations and of pathogenetic concepts. Hum Mutat 2010;31:1090-6.
16. Lefévre C, Audebert S, Jobard F, Bouadjar B, Lakhdar H, Boughdene-Stambouli O, et al. Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. Hum Mol Genet 2003;12:2369-78.
17. Parmentier L, Clepet C, Boughdene-Stambouli O, Lakhdar H, Blanchet-Bardon C, Dubertret L, et al. Lamellar ichthyosis: further narrowing, physical and expression mapping of the chromosome 2 candidate locus. Eur J Hum Genet 1999;7:77-87.
18. Parmentier L, Lakhdar H, Blanchet-Bardon C, Marchand S, Dubertret L, Weissenbach J. Mapping of a second locus for lamellar ichthyosis to chromosome 2q33-35. Hum Mol Genet 1996;5:555-9.
19. Ozdemir A, Korkut S, Kurtoglu S, Hatipoglu N, Gunes T, Ozturk MA. Neonatal endocrinologic problems in Collodion babies. Pediatr Dermatol 2017;34:290-4.
20. Fowler AJ, Moskowitz DG, Wong A, Cohen SP, Williams ML, Heyman MB. Nutritional status and gastrointestinal structure and function in children with ichthyosis and growth failure. J Pediatr Gastroenterol Nutr 2004;38:164-9.