Chung Shan Medical Journal 2024; 35:43-48

airiti

Case Report

Management of collodion baby with ABCA12 gene mutation and harlequin ichthyosis

Shih-Ching Lo[1,2,3], Hsing-Chun Lin[2,3], Xing-An Wang[4*]

[1] *Institute of Medicine, Chung Shan Medical University, Taichung City, Taiwan*
[2] *Department of Nutrition, Chung Shan Medical University Hospital, Taichung City, Taiwan*
[3] *Department of Nutrition, Chung Shan Medical University, Taichung City, Taiwan*
[4] *Department of Pediatrics, Chung Shan Medical University Hospital, Taichung City, Taiwan*

Harlequin ichthyosis (HI) is a rare and severe form of ichthyosis. Lamellar ichthyosis is more common in Taiwan with an incidence rate of 1/300,000~500,000. The transglutaminase 1 (TGM1) gene mutation is associated with cornification disorders, while the mutation of the lipid transporter adenosine triphosphate binding cassette A12 (ABCA12) gene is associated with a higher mortality rate. We present a case of collodion baby (CB) with autosomal recessive congenital ichthyosis (ARCI), harlequin ichthyosis (HI) type. This case report draws attention to the problems encountered during the management of infants with HI. Following holistic health care, he was healthy and discharged with rehabilitation carried out in outpatient clinic. Symptoms of HI vary from person to person. This patient presented with congenital ichthyosiform erythroderma, ectropion, and depressed nasal ridge with normal hearing. More case reports that detail the management of HI may help to improve medical treatment and outcomes.

Keywords: Harlequin Ichthyosis; adenosine triphosphate binding cassette A12; autosomal recessive congenital ichthyosis; Dermatology; Pediatrics

1. Introduction

In general, normal epidermal differentiation and functional skin barrier are characteristic of healthy skin. Harlequin ichthyosis (HI) can usually be differentiated from the less severe collodion baby (CB) phenotype based on clinical appearance. Classic skin changes of CB are more translucent and waxy, ectropion, and eclabium are often present in patients with CB, but are generally much less severe (1). Mutations in the genes transglutaminase 1 (TGM1), arachidonate lipoxygenase 3 (ALOXE3), or arachidonate 12-lipoxygenase, 12R type (ALOX12B) are involved in most cases of collodion babies (2). HI is a rare and severe form of keratinizing skin disorders. Mutations in the A12 lipid transporter adenosine triphosphate binding cassette (ABCA12) cause HI. Due to reduced transfer of lipids into lamellar granules, the stratum corneum is remarkably thickened and does not desquame (3). Patients may present with skin abnormalities, poor hair growth, nail deformities, ophthalmological problems, malnutrition, inflammatory arthritis, developmental delay, and respiratory problems (4). Recently, dysregulated pathways in the skin of HI patients have been identified feasible therapeutic targets.(5) We share our experience of managing a patient with HI.

* Correspondence Author: Xing-An Wang
Address: No. 110, Sec. 1, Jianguo N. Rd., Taichung City, 40201, Taiwan
Tel: +886-4-2473-9595 ext. 34301
E-mail: win1227.tw@yahoo.com.tw; mygodway@gmail.com

2. Case presentation

A male infant of gestational age 36 weeks +

airiti

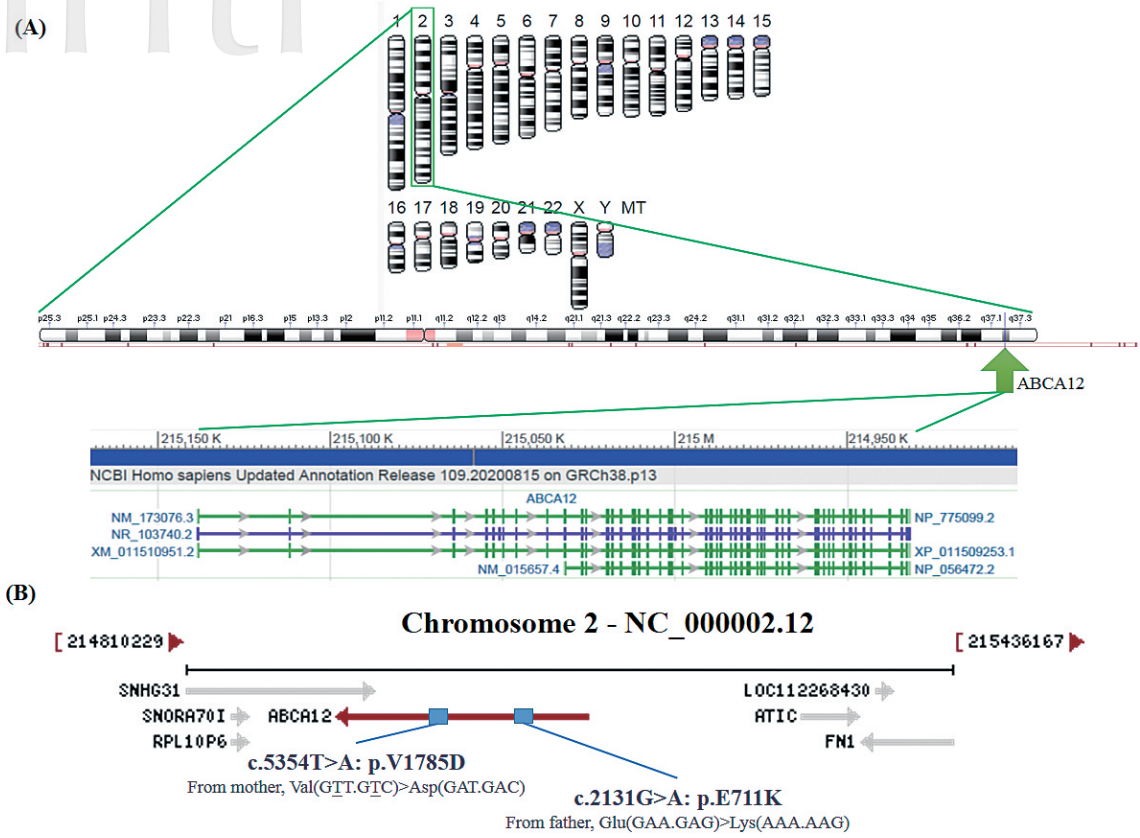


Figure 1. (A) ATP binding cassette subfamily A member 12 (ABAC12) genomic sequence (B) Heterozygous mutation c.5354T> A from mother and c.2131G>A from father, leading to changes in amino acid p.V1785D and p.E711K

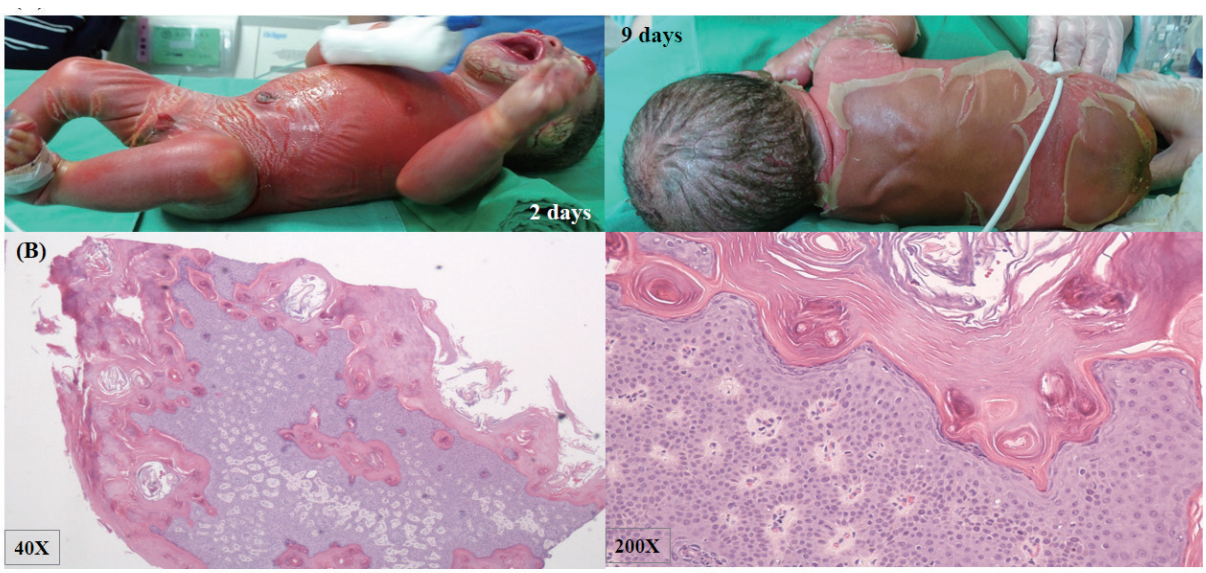


Figure 2. (A)At 2 days and 9 days post-birth. (B)Skin specimen is from the right leg and consists of light brown to tan formalin fixed tissue measuring 0.5 x 0.4 x 0.3 cm. Hematoxylin-Eosin stain, 40X and 200X.

airiti

1 day was born on 10 April 2018 at 16:25, with a maternal birth history of G2P2. He was delivered via normal spontaneous delivery. The birth weight was 2820 g, the head circumference was 32.5 cm the body length was 47 cm, and chest circumference 33 cm. Anthropometric measures at birth both 3rd-15th centile. The Apgar score was 7 in the first minute and 8 in the fifth minute after birth. He presented severe desquamation and was transferred to the neonatal intensive care unit (NICU). The mother, who is from Indonesia, received regular prenatal care with no signs of pregnancy-induced hypertension or gestational diabetes mellitus. Her prenatal group B streptococcus (GBS) culture was negative and she reported no smoking or alcohol or drug abuse. Pedigree showed that she had a son with her ex-husband but she denied any prior disease. Bilateral ectropion and ear malformation, genital ambiguity, and general skin tension and dryness were observed. The initial impression was CB (2). Genetic analysis did not show a mutation in the TGM1 gene and chromosome study indicated karyotype of normal male (Supp. Fig. 1). After consulting a dermatologist, the impression was CB with autosomal recessive congenital ichthyosis (ARCI), HI type. Two years later, ABCA12 gene mutation (Figure 1A; father: c.2131G>A: E711K, mother: c.5354T>A: V1785D, patient: c.5354T>A: V1785D/c.2131G>A: E711K) was confirmed in the diagnosis of HI (Figure 1B).

According to the literature (1) management of HI in the neonatal period should focus on minimizing transepidermal water loss (TEWL) by placing the infant in isolette with humidity set at 50-70%. In addition, adequate calories and protein should be provided for low-weight infants. Enteral feeding infant formula 5 c.c. every 3 hours with parenteral nutrition (PN) provides 39.6 kcal/kg and 2.55 g/kg protein. The widespread hyperkeratotic lesions with fissure wounds require treatment. Neomycin ointment for creases and Locasalen ointment for focal and topical application to thick, yellowish, plate-like scales are recommended, taking care to avoid open wounds.

Plain film radiography showed a prominence of bilateral lung marks, possibly due to inadequate inspiration. Ampicillin and Fortum were prescribed for antibiotic prophylaxis. The infant's vital signs and general condition were closely monitored. There was a shiny waxy-looking outer layer of skin covering the body with bleeding from the creases at the abdomen and in the bilateral inguinal areas and axilla. Gradually increase enteral nutrition 5 c.c. per meal every day as tolerable. Skin biopsy from the right thigh and microscopic examination of skin showed epidermal hyperplasia, accompanied by apparently dense hyperkeratosis (Figure 2B). At 9 days post-birth, light microscopy showed normal hair and new skin formation with shiny stratum corneum and underlying generalized erythroderma (Figure 2A). Oral feeding infant formula 35 c.c. every 3 hours with PN total achieved 109.9 kcal/kg and 3.8 g/kg protein daily. One month later, there was significant improvement in collodion membrane formation over scalp, face, trunk, and extremities. Weaned PN and oral feeding 100 c.c. per 4 hours, maintained daily goal calories 143 kcal/kg with protein 2.99 g/kg.

3. Results

At 35 days post-birth, TSH (24.89), T3 (169.1), and T4 (7.94) levels were indicative of congenital hypothyroidism. The results of thyroid scan conducted at 43 days post-birth suggested dyshormonogenesis (Supp. Fig. 2). After treatment of endocrinological abnormalities and a recheck of thyroid data, TSH (1.97), T3 (171.1), and T4 (7.83) appear to be normal. Acitretin 1mg/kg was administered after receiving the genetic analysis report with stabilization and improvement of the cutaneous condition. Although the infant presented with poorly developed ears and small canals, he passed newborn hearing automated auditory brainstem response (AABR) screening at 59 days post-birth. Finally, his condition improved and he became stable after intensive care. He was discharged at 80 days post-birth and followed up in outpatient clinic.

4. Discussion and conclusion

At first, we did not consider that the patient was of HI type because the last case was found about 20 years ago. There are several CBs with lamellar ichthyosis in Taiwan every year, but reports of HI type are rare. There are only 2 patients who have survived with regular rehabilitation in local clinics.

airiti

CHROMOSOME STUDY REPORT

Culture No. BC-20180398

CHROMOSOME COUNTS：

45	46	47	other	total
	20			20



Tissue Examined: Blood

Analyze: 4 cells

Karyotype: 4 cells

Date of Culture：2018/04/11

Date of Report：2018/04/18

Method：

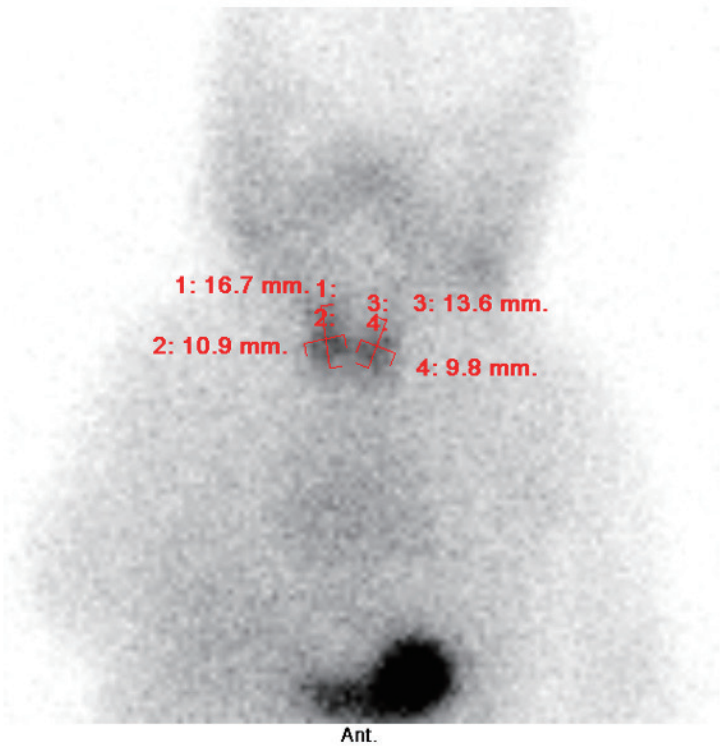
Result：46,XY

STAINING METHOD：* GIEMSA BANDING __ C BANDING __ NOR

INTERPRETATION

The karyotype shows a male chromosome complement. Although the accuracy of this cytogenetic testing is very high, the possibility that chromosomal abnormalities not detectable by current culture and staining techniques can not be excluded.

Supplementary Figure 1. Chromosome study report.



Supplementary Figure 2. Thyroid scan shows inhomogeneous distribution of radioactivity in both lobes (right lobe measures 1.7 x 1.1 cm, left lobe measures 1.4 x 1.0 cm).

Prior experience indicated intensive care and early introduction of oral retinoids increased the survival rate (4). ARCI is a heterogeneous group of non-syndromic disorders of keratinization, including

airiti

lamellar ichthyosis (LI), congenital ichthyosiform erythroderma (CIE), and HI (2). HI is caused by autosomal recessive mutations in ABCA12 (6), which encodes a member of a large superfamily of ATP-binding cassette transporters. ABCA12 works in the transport of lipids into the trans-Golgi network and lamellar granules, for the accumulation of lipids that are essential for the formation of the skin barrier. A severe ABCA12 deficiency causes defective lipid transport, resulting in malformation of the intercellular lipid layers at the interface of the granular-cornified layer and disruption of the epidermal lipid barrier (7). 3D imaging may help prenatal diagnosis of HI. Obtaining an early sonographic diagnosis of HI is difficult. Short feet and extremely hyperflexed toes can be an early marker of HI, 3D imaging is essential to understand 2D images and enabling diagnosis of HI (8). More case reports can lead to better medical treatment and results.

Acknowledgements

We would like to thank all the participating investigators and the directors of the nutrition and pediatric departments of CSMUH who served as scientific advisors.

Conflict of interests:

The authors have no conflicts of interest to report.

References

1. 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(1).
2. Prado R, Ellis LZ, Gamble R, Funk T, Arbuckle HA, Bruckner AL. Collodion baby: an update with a focus on practical management. Journal of the American Academy of Dermatology. 2012;67(6):1362-74.
3. Hovnanian A. Harlequin ichthyosis unmasked: a defect of lipid transport. The Journal of clinical investigation. 2005;115(7):1708-10.
4. 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. Archives of dermatology. 2011;147(6):681-6.
5. Enjalbert F, Dewan P, Caley MP, Jones EM, Morse MA, Kelsell DP, et al. 3D model of harlequin ichthyosis reveals inflammatory therapeutic targets. The Journal of clinical investigation. 2020;130(9):4798-810.
6. Kelsell DP, Norgett EE, Unsworth H, Teh MT, Cullup T, Mein CA, et al. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. American journal of human genetics. 2005;76(5):794-803.
7. Shibata A, Akiyama M. Epidemiology, medical genetics, diagnosis and treatment of harlequin ichthyosis in Japan. Pediatrics international : official journal of the Japan Pediatric Society. 2015;57(4):516-22.
8. Vijayakumari M, Reddy DK, Routhu M, Vuchuru M, Reddy NS. Prenatal diagnosis of harlequin ichthyosis: a case report. Obstetrics & gynecology science. 2020;63(1):94-7.