International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-3, 2015 ISSN No: 2277 - 7873

REVIEW ARTICLE

A Review on Harlequin Ichthyosis

Humeera Rafeeq*, Osman Ahmed, Fayeeza Ameen, Amreen Sultana, Maryam Fatima

Deccan School of Pharmacy, Hyderabad –01, T.S, India.

Manuscript No: IJPRS/V4/I3/00161, Received On: 19/08/2015, Accepted On: 28/08/2015

ABSTRACT

It is the severe genetic disorder affecting the skin. Infants with this disorder are born with thick and hard skin almost covering the entire body. On the skin deep cracks are formed separating diamond shaped skin as plates. The eyelids, ears, mouth and nose are affected by these skin abnormalities limiting the movements of arms and legs. Chest movements are also restricted leading to difficulties in breathing and respiratory failure. Due to various complications like dehydration related, infectious and respiratory problems, the newborn infants die usually at first days of life. Harlequin ichthyosis is caused by the mutations in *ABCA12* gene. A protein which is essential for the developing of skin cells is instructed for making by the *ABCA12* gene. Transport of lipids is majorly caused by this protein into the outermost layer i.e. epidermis. *ABCA12* protein making is been prevented by the mutations occurring in *ABCA12* gene. It was demonstrated that Harlequin ichthyosis occurs mainly due to the loss of *ABCA12* functional mutations, which involves in the coding of lamellar granule membrane proteins which are involved in lipid transport. Severe dysregulation of cornification is resulted from loss of *ABCA12* expression in humans, resulting in coverage of infants in armor of lethal type. Based on these findings and our ability to offer mutational screening and early DNA-based prenatal diagnosis of Harlequin ichthyosis shall be dramatically improved.

KEYWORDS

Harlequin Ichthyosis, *ABCA12* Gene, Lipid Transport, Stratum Corneum

INTRODUCTION

Harlequin Ichthyosis

It is the severe genetic disorder affecting the skin. Infants with this disorder are born with thick and hard skin almost covering the entire body. On the skin deep cracks are formed separating diamond shaped skin as plates. The eyelids, ears, mouth and nose are affected by these skin abnormalities limiting the movements of arms and legs. Chest movements are also restricted leading to difficulties in breathing and respiratory failure.

***Address for Correspondence:**
Ms. Humeera Rafeeq
Deccan School of Pharmacy,
Dar-Us-Salam, Agapura, Nampally,
Hyderabad, Telangana State, India.
E-Mail Id: humeerarafeeq@gmail.com

In between the environment and the body, the skin normally acts as a protective barrier. This skin barrier is been disrupted in Harlequin ichthyosis leading to difficulty for the infants for controlling the water loss from the body, regulating the body temperature and for fighting infections.

Dehydration occurs often due to excessive loss of body fluids in infants developing life threatening infections at first week of birth. It is very rare for the new born to survive with the Harlequin ichthyosis. However, with advanced medical and improvement treatment methods, there are increased chances for the affected people of living up to adolescence.[1]

Relation of *ABCA12* Gene with Harlequin Ichthyosis

Harlequin ichthyosis is caused by the mutations in *ABCA12* gene. A protein which is essential for the developing of skin cells is instructed for making by the *ABCA12* gene. Transport of lipids is majorly caused by this protein into the outermost layer i.e. epidermis. *ABCA12* protein making is been prevented by the mutations occurring in *ABCA12* gene. Other mutations results in production of abnormal proteins which are unable to transport lipids properly. *ABCA12* protein loss functionally leads to disturbances in normal development of skin which results in thick and hard characteristic scales of Harlequin ichthyosis.[1]

A Defect in Lipid Transport – A Major Cause for Harlequin Ichthyosis

The Harlequin ichthyosis was first described in United State in 1750 at Reverend Oliver Hart.[2] It was believed for its inherition in autosomal-recessive manner, and the Harlequin ichthyosis affected infants are encased in thick, yellow scale plate- armor with red fissuring. Normal appearance of face is lost due to tight pulling of the skin giving a frog like appearance with eyelids and lips everted (ectropion, eclabion) and the nose and ears get flattened. Swollen extremities are formed due to massive thickening leading to constriction of the skin. Due to various complications like dehydration related, infectious and respiratory problems, the newborn infants die usually at first days of life. On treatment with vitamin A derivatives, retinoid some patients survived leading to development of severe ichthyosis. However the cause of Harlequin ichthyosis is difficult to know and till now late prenatal diagnosis is depended on the electron microscopic examination of the tissue sampled by means of biopsy of invasive fetal skin.

Mutational Changes in *ABCA* Gene Disrupting the Lipid Transport

From the *ABC* transporter protein family, the members of *ABCA* subclass bind to the ATP to facilitate the active transport of the lipids through the cell membrane against their concentration gradients. In tangier disease *ABCA1* has been proven to be the gene causing it. Tangier disease is the disorder which occurs due to the transport of the cholesterol between liver and the various other tissues.[3-6], *ABCA4* which is expressed exclusively for transport of retinol in the photo receptors of eye, the mutations in *ABCA4* leads to Stargardt disease, Cone-rod dystrophy or Recessive retinitis pigmentosa, in which retinods abnormal accumulation leads to the development in macular dystrophy resulting in loss of central vision.[7-9]

For the protection of most outermost layer of the skin i.e. stratum corneum, the lipid processing within the skin is essential.[10] Corneum cells i.e. the corneocytes are attached with each other by means of corneodesmosomes forms a cornified layer embedded in the intercellular lipid lamellae, this layer acts as a barrier for body defense between the external and internal environment. From the lamellar granules i.e. the highly rich lipid organelles which are been present in the epidermal granular cells derive the lipid lamellae. These epidermal granular cells are originated from trans-Golgi complex. Polar lipids i.e. the cholesterol sulfate, sphingomyelin, glucosylceramides and the phospholipids which acts as precursors for the stratum corneum intercellular lipids are present in the lamellar granules. Apart from the lipids, the transporting of proteases with its inhibitors and lipid-processing enzymes is done by lamellar granules. All these lipid processing enzymes and proteases along with its inhibitors play a major role in controlling of desquamation process and barrier permeability.[11] Acid hydrolases, β-glucocerebrosidase, secretory phospholipase A2 and acid sphingomyelinase come under the lipid processing enzymes. At the junction of the first stratum corneum layer and the granular layer, the lamellar granules are normally fused with the apical surface of the cell and discharge the lipids contents into the intercellular space resulting in the complex changes of lipid composition by means of these enzymes actions for the formation of lipid lamellae of stratum corneum. The equimolar mixture of cholesterol, free fatty acids and ceramides is present in the lipid lamellae.

Very effective protection is provided by these structures against fluid loss and external aggressions.

In previous study the lamellar granules were revealed which were either abnormal or absent possessing no intercellular lamellae, studied in Harlequin ichthyosis by electron microscopy.[12] by this data it was suggested that the defect in lamellar granules results in stratum corneum thickening and leading to armor like scales accumulate in Harlequin ichthyosis. These events on basis of genetics have not been explained.

Various types of defects in the lipid processing enzymes which cause several forms of Harlequin ichthyosis are-

a. Defects in steroid sulfatase in the X-linked recessive ichthyosis.[13]
b. Defect in β-glucocerebrosidase in the Gaucher disease.[14]
c. Defects in sphingomyelinase in the Niemann-Pick disease[15]
d. Defects in fatty aldehyde dehydrogenase in the Sjögren-Larsson disorder.[16]
e. Defects in 12R-lipoxygenase and lipoxygenase-3 in autosomal-recessive congenital ichthyosis.[17]
f. Defects in CGI-58 in the Chanarin-Dorfman disorder.[18]

None of this ichthyosis is as severe as Harlequin ichthyosis, they explain or figure out that a major role for lipid abnormalities exists in the ichthyosis pathgophysiology.

Expression of Mutations in *ABCA12*

Akiyama et al. demonstrated that Harlequin ichthyosis occurs mainly due to the loss of *ABCA12* functional mutations, which involves in the coding of lamellar granule membrane proteins which are involved in lipid transport. According to the knowledge that *ABCA1* mutations and *ABCA4* mutations respectively causes Tangier disease and Stargardt disease, this further discovery sheds light onto the lipid processing importance in maintenance and development of the epidermal barrier.

Akiyama et al. due to lamellar granule abnormalities observation in epidermal keratinocytes oh Harlequin ichthyosis patients led him to test the hypothesis that defects in the major lamellar granule protein could become defective in Harlequin ichthyosis.[19] A parallel graph is drawn between *ABCA12* harboring the missense autosomal recessive congenital ichthyosis mutations and the *ABCA3* protein.[20] *ABCA3* encodes a lamellar granule membrane protein which is essential for the secretions in lung cells and the transport of alveolar surfactant lipid[21]. Based on the hypothesis saying that mutations in *ABCA12* are more deleterious than that of those leading to autosomal recessive congenital ichthyosis and it was proved to be correct. They explained that 5 different mutations in *ABCA12* have been resulting in the truncation or deletion of *ABCA12* protein highly conserved regions, which disrupt the lipid transport across membrane. Based on homozygosity mapping, Kelsell et al. used a completely distinct genomic approach involving the single nucleotide polymorphism chip technology for the identification of *ABCA12* as the major causative gene in Harlequin ichthyosis.[22]

Akiyama et al. discovered on the consequence of impaired *ABCA12* functioning, and stressed on the lamellar granules, which were not formed properly and hence lipids which are essential for stratum corneum formation like glucosylceramide were processed abnormally, diffusely distributed, and not secreted or secreted abnormally. Hence the extra ordinary thickening of stratum corneum was due to abnormal barrier formation mainly caused by the lack of lipid lamellae.[19]

Implications for Therapy and Prenatal Diagnosis

Genetic correction of *ABCA12* was also showed by Akiyama et al. *ABCA12* deficiency was by the gene transfer in the patients. Lamellar granule formation and normal cell distribution of glucosylceramide were restored by keratinocytes. This results in the increased possibility of Harlequin ichthyosis treatment by means of systemic administration of *ABCA12* gene or

ABCA like properties along with the functional peptides, this delivery approaches are done or carried out either prior or after the child birth.[19]

ABCA12 role discovery in Harlequin ichthyosis reveals that it plays a major role for the transport of lipid in the skin barrier formation and its functioning. This is a very important considered to be as an explanation for the adaptive evolution of terrestrial life which involves *ABCA3* and *ABCA12* (*two lipid transporters which are closely related*), which are necessary for alveolar surfactant production and lipid lamellae of the stratum corneum. *ABCA3* at birth prevents the collapsing of the lungs. *ABCA12* provides protection to skin from water loss and external aggressions. Severe dysregulation of cornification is resulted from loss of *ABCA12* expression in humans, resulting in coverage of infants in armor of lethal type.[19]

CONCLUSION

Based on these findings and our ability to offer mutational screening and early DNA-based prenatal diagnosis of Harlequin ichthyosis can be dramatically improved and will also allow us for the development of new and specific therapeutic approaches for the effective studying, to make the treatment of Harlequin ichthyosis more reliable and easy.

REFERENCES

1. *Harlequin ichthyosis*. Genetics Home Reference. Available at- http://ghr.nlm.nih.gov/condition/harlequinichthyosis
2. Waring, J. I. (1932). Early mention of a harlequin fetus in America. *American Journal of Diseases of Children*, *43*(2), 442-442.
3. Bodzioch, M., Orsó, E., Klucken, J., Langmann, T., Böttcher, A., Diederich, W., & Schmitz, G. (1999). The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. *Nature Genetics*, *22*(4), 347-351.
4. Brooks-Wilson, A., Marcil, M., Clee, S. M., Zhang, L. H., Roomp, K., van Dam, M., & Hayden, M. R. (1999). Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. *Nature Genetics*, *22*(4), 336-345.
5. Rust, S., Rosier, M., Funke, H., Real, J., Amoura, Z., Piette, J. C., & Assmann, G. (1999). Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. *Nature Genetics*, *22*(4), 352-355.
6. Remaley, A. T., Rust, S., Rosier, M., Knapper, C., Naudin, L., Broccardo, C., & Brewer, H. B. (1999). Human ATP-binding cassette transporter 1 (ABC1): genomic organization and identification of the genetic defect in the original Tangier disease kindred. *Proceedings of the National Academy of Sciences*, *96*(22), 12685-12690.
7. Martínez Mir, A., Paloma, E., Allikmets, R., Ayuso, C., Río, T. D., Dean, M., & Balcells, S. (1998). Retinitis pigmentosa caused by a homozygous mutation in the Stargardt disease gene ABCR. *Nature Genetics*, *18*(1), 11-12.
8. Rozet, J. M., Gerber, S., Ghazi, I., Perrault, I., Ducroq, D., Souied, E., & Kaplan, J. (1999). Mutations of the retinal specific ATP binding transporter gene (ABCR) in a single family segregating both autosomal recessive retinitis pigmentosa RP19 and Stargardt disease: evidence of clinical heterogeneity at this locus. *Journal of Medical Genetics*, *36*(6), 447-451.
9. Cremers, F. P., van de Pol, D. J., van Driel, M., den Hollander, A. I., van Haren, F. J., Knoers, N. V., & Hoyng, C. B. (1998). Autosomal recessive retinitis pigmentosa and cone-rod dystrophy caused by splice site mutations in the Stargardt's disease gene ABCR. *Human Molecular Genetics*, *7*(3), 355-362.
10. Madison, K. C. (2003). Barrier function of the skin: “la raison d'etre” of the epidermis. *Journal of Investigative Dermatology*, *121*(2), 231-241.

11. Elias, P. M. (2004). The epidermal permeability barrier: from the early days at Harvard to emerging concepts. *Journal of Investigative Dermatology*, *122*(2), xxxvi-xxxix.

12. Milner, M. E., O'Guin, W. M., Holbrook, K. A., & Dale, B. A. (1992). Abnormal lamellar granules in harlequin ichthyosis. *Journal of Investigative Dermatology*, *99*(6), 824-829.

13. Shapiro, L., Weiss, R., Webster, D., & France, J. (1978). X-linked ichthyosis due to steroid-sulphatase deficiency. *The Lancet*, *311*(8055), 70-72.

14. Sidransky, E., Tsuji, S., Martin, B. M., Stubblefield, B., & Ginns, E. I. (1992). DNA mutation analysis of Gaucher patients. *American Journal of Medical Genetics*, *42*(3), 331-336.

15. Schmuth, M., Man, M. Q., Weber, F., Gao, W., Feingold, K. R., Fritsch, P., & Holleran, W. M. (2000). Permeability barrier disorder in Niemann–Pick disease: sphingomyelin–ceramide processing required for normal barrier homeostasis. *Journal of Investigative Dermatology*, *115*(3), 459-466.

16. De Laurenzi, V., Rogers, G. R., Hamrock, D. J., Marekov, L. N., Steinert, P. M., Compton, J. G., & Rizzo, W. B. (1996). Sjögren–Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. *Nature Genetics*, *12*(1), 52-57.

17. Jobard, F., Lefèvre, C., Karaduman, A., Blanchet-Bardon, C., Emre, S., Weissenbach, J., & Fischer, J. (2002). Lipoxygenase-3 (ALOXE3) and 12 (R)-lipoxygenase (ALOX12B) are mutated in non-bullous congenital ichthyosiform erythroderma (NCIE) linked to chromosome 17p13. 1. *Human Molecular Genetics*, *11*(1), 107-113.

18. Lefèvre, C., Jobard, F., Caux, F., Bouadjar, B., Karaduman, A., Heilig, R., & Fischer, J. (2001). Mutations in CGI-58, the gene encoding a new protein of the esterase/lipase/thioesterase subfamily, in Chanarin-Dorfman syndrome. *The American Journal of Human Genetics*, *69*(5), 1002-1012.

19. Akiyama, M., Sugiyama-Nakagiri, Y., Sakai, K., McMillan, J. R., Goto, M., Arita, K., & Shimizu, H. (2005). Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. *Journal of Clinical Investigation*, *115*(7), 1777.

20. Lefèvre, C., Audebert, S., Jobard, F., Bouadjar, B., Lakhdar, H., Boughdene-Stambouli, O., & Fischer, J. (2003). Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. *Human Molecular Genetics*, *12*(18), 2369-2378.

21. Yamano, G., Funahashi, H., Kawanami, O., Zhao, L. X., Ban, N., Uchida, Y., & Inagaki, N. (2001). ABCA3 is a lamellar body membrane protein in human lung alveolar type II cells. *FEBS Letters*, *508*(2), 221-225.

22. Kelsell, P. D., Norgett, E. E., Unsworth, H., Teh, M. T., Cullup, T., Mein, C. A., & O'Toole, A. E. (2005). Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. *The American Journal of Human Genetics*, *76*(5), 794-803.

