Deletion in Exon-20 of *ABCA12* Gene Causing Harlequin Ichthyosis

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Abstract
Harlequin ichthyosis is a rare form of congenital ichthyosis and affects 1 in 300,000 live births. Both antenatal sonography and early molecular diagnosis are essential for precise genetic counseling and prognostication. Moreover, this information will also help parents to understand the need for prenatal genetic testing for future pregnancies.

Keywords
Genetics, Harlequin, Ichthyosis

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Introduction

Harlequin ichthyosis (HI) is an extremely rare form of congenital cutaneous disorder of abnormal epidermal differentiation, characterized by cutaneous scaling in addition to systemic manifestation. HI is associated with mutation of the lipid transporter adenosine triphosphate-binding cassette subfamily a member 12 (*ABCA12* gene).[1]

Case Report

A 28-year-old Gravida 2, Abortion 1 mother delivered a 1940 g girl at 34 weeks of gestation. Antenatal scan done at 31 weeks of gestation showed persistently open mouth with protruding tongue, periorbital edema, and restricted fetal joint movements. Baby was born by normal vaginal delivery, cried immediately, and was encased in an "armor" of thick keratotic scale plates separated by deep fissures at birth. There was bilateral ectropion and eclabium along with flattened nose and ears that appeared rudimentary. There were constricting bands around the extremities that were sufficient enough to restrict movement and cause digital necrosis.

Management of such neonates[2,3] requires an integrative approach including family members, nursing staff, neonatologist, and dermatologist. She was nursed in an incubator for initial few days to provide a humidified temperature-controlled environment. Twice daily bathing by wetting roll gauze with warm sterile water was done and once application of glycerin and paraffin gauze was done in every nursing shift. Umbilical line was secured to maintain adequate fluid balance. She developed hypernatremia (serum sodium: 158 mmol/L) at 44 h of life that was managed through fluid resuscitation as per the hypernatremia protocol. She was given intravenous acetaminophen for pain, and lubricating eye ointment was applied to prevent ocular complications because of ectropion. Acitretin, an oral retinoid was started at a dose of 1 mg/kg/day orally along with vitamin D supplementation. Acitretin therapy hastens shedding of the hyperkeratotic skin and its continued usage helps in releasing the constrictions that can improve the function of the involved region. Postnatal clinical exome sequencing in our case detected homozygous single base pair deletion in exon 20 of the *ABCA12* gene (chr2: g.215004283del; depth: 142x) that results in a frameshift and premature truncation of the protein 7 amino acids downstream to codon 870 (p.Pro870LeufsTer7; ENST00000272895.12). Parents were heterozygous for the same mutation. Orogastric feeding could be started by day 9 of life and discharged on assisted feeding on day 16 of life.

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Mother was trained specifically regarding skin care, eye care, and maintenance of hygiene.

Discussion

There are a very few cases of HI reported in the medical literature. In the past, HI was almost a fatal disease; however, with recent advances in neonatal intensive care along with multidisciplinary management, many infants have better long-term survival.[3] Prenatal ultrasonographic features like eclabium (eversion of lips), ectropion (outturning of eyelid), contractures, and snowflake sign (floating skin particles in amniotic fluid) are indicators toward the diagnosis of HI; however, these are not detectable until the second trimester.[2-4] Affected babies are generally born premature and are encased in a markedly thickened and hard stratum corneum described as armorlike skin. Such thickened skin can cause pseudocontractures resulting in limited joint movements and impaired perfusion that can further lead to digital necrosis.[3] Soon after birth, this casing cracks and results in a deep transverse and longitudinal fissure. Other typical facial features include eclabium, ectropion, flattened ear and nose, and edematous limbs. Barrier function of the skin is compromised and has decreased ability to protect against bacterial, chemical, and mechanical assault with impaired thermoregulation and increased risk for hypernatremic dehydration and sepsis. Metabolic demand is also increased because of increased skin turn over and increased transepidermal water loss.[3]

Pathophysiology behind HI is a mutation in the lipid transporter adenosine triphosphate binding cassette A12 (*ABCA12*). This transporter facilitates delivery of lipid glucosylceramides into the lamellar granules which is then further delivered to extracellular space. Mutations in *ABCA12* have been known to cause autosomal recessive congenital ichthyoses that includes congenital ichthyosiform erythroderma, lamellar ichthyosis, and HI, which is the most severe phenotype.[2,3] A total of 62.5% of reported *ABCA12* mutations are expected to result in truncated proteins. Most mutations in HI are truncation mutations, and homozygous or compound heterozygous truncation mutations always result in HI phenotype.[1] Till date 51 mutations in *ABCA12* have been found to be associated with HI and the most common mutation is c.7322delC (p.Val2442SerfTer28) in exon 49.[1,2] Postnatal clinical exome sequencing in our case detected homozygous single base pair deletion in exon 20 of the *ABCA12* gene (chr2: g.215004283 del; depth: 142x) that results in a frameshift and premature truncation of the protein 7 amino acids downstream to codon 870 (p.Pro870LeufsTer7; ENST0000 0272895.12). The g.215004283del (p. Pro870LeufsTer7) mutation in exon 20 has not been reported in the literature. The same variant was detected in the heterozygous state of both parents.

HI is recognized at birth by typical clinical features, and genetic testing is essential for confirming the diagnosis. It is helpful for a precise genetic counseling and prognostication and can serve as a guide for future family planning. Identifying parental carrier status allows for DNA-based prenatal genetic diagnosis in future pregnancy. Most infants initially could be managed with liquid paraffin, topical eye lubricants/antibiotics, paracetamol for pain relief, and oral retinoids that help in shedding of the grossly thickened skin.[2-4]

Conclusion

HI is a rare form of congenital ichthyosis that can present many challenges throughout a lifetime, but especially during the neonatal period. An understanding of the disrupted barrier in these patients forms the basis of aggressive and supportive care from an interdisciplinary team for effective management.

Declaration of Conflicting Interests

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