Case Report

Siblings with congenital ichthyosis – A case report

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ABSTRACT

Ichthyosis is a disorder of cornification characterized clinically by patterns of scaling and histopathological features of hyperkeratosis. Harlequin ichthyosis (HI) is caused by mutations in the ABCA12 gene which is responsible for the development of a normal skin barrier. Babies with HI have characteristic clinical features such as markedly thickened, cracked, and ridged skin forming horny armor-like plates over the entire body. This causes facial disfigurement in form of ectropion, chemosis of orbits, and fish-like mouth flat nose crumbled ears. Limb joints become fixed, digits are constricted, nails and hair may be absent. Affected patients have high morbidity and mortality due to respiratory difficulty, poor feeding, and skin infections.

Key words: Cornification disorders, Harlequin ichthyosis, Hyperkeratosis

Ichthyosis is caused due to abnormal epidermal differentiation. It could be acquired or inherited. The common inherited variety is subdivided as autosomal dominant or recessive [1]. Harlequin ichthyosis (HI) is severe a fatal form of autosomal recessive type of congenital ichthyosis [2]. The incidence is very low ~1 in 200,000 births [3]. The affected newborn has a typical grotesque appearance with, encased thick, large, thick grayish-yellow armor-like skin plaques with reddish moist oozing cracks all over the body. Other features include a severe bilateral ectropion, eclabium, flattened and crumbled ears, malformed nose, and semi-flexed extremities due to restricted joint mobility, and absent or hypoplastic nails. Scalp hair, eyebrows, and eyelashes are usually absent [1,4,5]. We are presenting this rare devastating gene dermatoses encountered in two siblings from our tertiary health care institute.

CASE REPORT

Case 1 (Elder Sibling)

A Preterm male child was born to 22-year-old mother at 35 weeks of gestation with uneventful antenatal history. His birth weight was 2.3 kg. At birth, the neonate was covered with thick armor-like rigid yellowish-grayscales with deep crevices (Fig. 1a). He had typical facial features of HI with a fish configuration of mouth, ectropion, his nose was small with constricted nostrils, bilateral crumbled ears (Fig. 1a). The hands and feet were swollen and edematous. Fingers and toes were claw-like, they were clenched and fixed in flexed position. Nails were rudimentary (Fig 1b and 2b) All joints had contractures due to thick skin. The baby was hospitalized after birth and started on intravenous fluids, oral feedings by nasogastric tube antibiotics, and emollients as per dermatology advice. Deoxyribonucleic acid (DNA) testing of this baby had shown AR type of HI involving the ABCA12 gene. He deteriorated overtime and died of sepsis on day 7.

Case 2 (Younger Sibling)

The younger male sibling was born when mother was 23 years old, antenatal history was uneventful. The baby was born preterm with gestation of 34 weeks. His birth weight was 1.9 kg. He also had a similar clinical profile as the elder sibling (Fig. 2a). Like the elder sibling, this baby also had a fish configuration of mouth, ectropion, nose was small with constricted nostrils, bilateral crumbled ears, edematous hands and feet, claw-like fingers and toes, rudimentary nails (Fig. 2b). All joints had contractures due to thick skin. In addition to the above features, this baby had amputations of toes in the left foot (Fig. 2b). After birth, the child was hospitalized, started on intravenous fluids, antibiotics, and emollients. This baby got successfully discharged on emollients. Parents were explained about the guarded prognosis. At 3 months of follow-up, this baby is doing well.

DISCUSSION

Mendelian disorders of cornification (ichthyoses) are a primary group of inherited conditions characterized clinically by patterns

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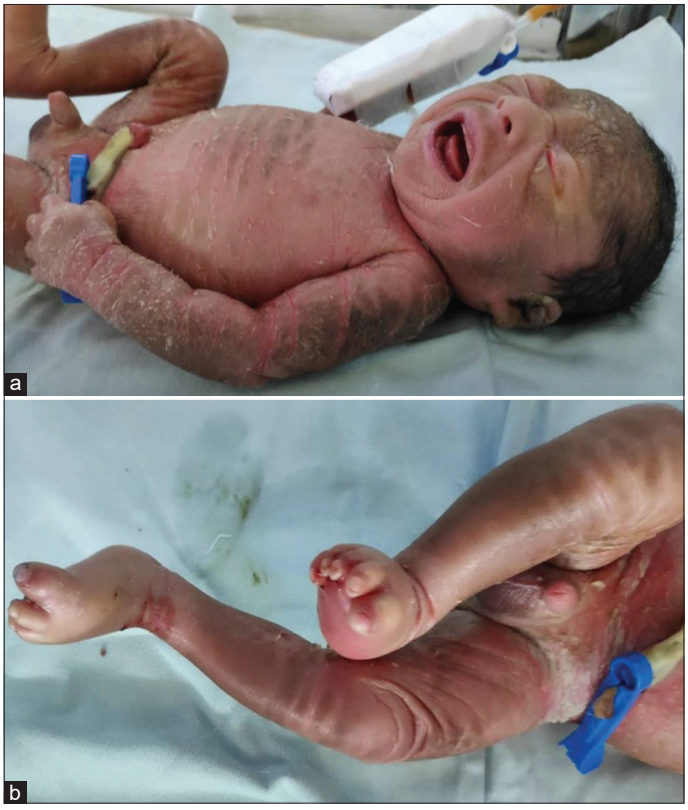

Figure 1: (a) First sibling with thick armor like, rigid yellow scales with deep crevices and ectropion; (b) contractures at knee, ankle, and interphalangeal joints of toes with hypoplastic nails

Figure 2: (a) Second sibling with thick armor like, rigid yellow scales with deep crevices; (b) contractures at knee, ankle, and interphalangeal joints of toes with hypoplastic nails and amputation of the left foot toes

of scaling and histopathological features of hyperkeratosis. They are usually distinguishable based on the inheritance patterns, clinical features, associated defects, and histopathologic changes.

The term ichthyosis is derived from the Greek word "Ichthys" meaning "fish" and refers to the similarity in appearance of the skin of ichthyosis patients to scaly fish skin [6]. The first Harlequin fetus was reported in 1750 by a clergyman named Oliver Hart, from Charleston, South Carolina, USA [7]. Ichthyosis is a Mendelian disorder of cornification which is a large, clinically, and etiologically heterogeneous group characterized by patterns of scaling and histopathologically by hyperkeratosis [1,8]. HI is an autosomal recessive type of ichthyosis with an incidence of around 1:300,000 [9].

Dysfunction of the epidermal barrier due to defective formation of intercellular lipid layers is the main cause of hyperkeratosis in HI. The formation of intercellular lipid layers is a highly complex process which includes the transport of lipids into the lamellar granules. Infants with HI either do not have these granules or have defective ones. This causes loss of barrier function and massive water loss through skin layers leading to hyperkeratosis. Many studies have found association between the losses of function mutations of the ABCA12 gene which codes for membrane-based lipid transporter protein and hyperkeratosis in HI [1,9,10].

HI can be diagnosed antenatally and postnatally. Antenatal diagnosis with positive family history involves fetal skin biopsy which can be done at 18 weeks of gestation. Chorionic villous sampling, amniocentesis, and the recent advances in antenatal ultrasonography have helped in the identification of fetal ichthyosis. Antenatal sonological features of ichthyosis include irregularity of skin surface, thickened scalp and abdominal wall, ectropion with eyelid chemosis, eclabium giving rise to fish mouth appearance, and restricted fetal movement with fixed limbs in semi-flexed position. Other limb abnormalities include claw-like hands that are unable to open, hypoplastic fingers, toes, and hypoplastic phalanges, and hyperechogenic amniotic fluid [11,12].

Postnatal diagnosis is mostly on clinical basis supported by genetic studies [4]. In our case, the genetic workup revealed ABCA12 mutation. Skin biopsy showed features like irregular thickening of the epidermis with hyperkeratosis and parakeratosis. Epidermal cells showed a clear space around the nuclei. Intradermal cleavage was visible with evidence of bacterial infection. Findings were consistent with the clinical diagnosis [4]. In the majority of cases, the affected fetus succumbs in the intrauterine period and a few are born alive. Newborn babies with HI have severe respiratory and feeding difficulties [1,2].

Clinical features of babies with HI are almost similar with markedly, thickened, cracked skin forming horny plates all over the body with red fissures like armor closely resembling a Harlequin's costume, hence the name [1,2,9]. These horny plates cause facial disfigurement and constriction of digits. Eyes have severe ectropion and chemosis obscuring the orbits. The nose and ears are flattened and crumbled, lips are everted and gaping. Hair and nails may be hypoplastic or absent. Hands and feet appear fixed and ischemic with restricted joint mobility [1,9]. Limited chest expansion along with coexisting skeletal deformity can lead to respiratory insufficiency. The risk of skin

infections is very high; hence, the majority of babies with HI die soon [9].

Early neonatal management of HI involves thermoregulation, adequate hydration, skincare and mucosa, adequate humidification, nutrition management, and sepsis control. Skincare involves gentle application of emollients over body to avoid transepidermal water loss and improve barrier function. Nutritional requirements can be fulfilled by tube feedings and intravenous fluids. Fluid and electrolyte imbalances have to be regulated with strict fluid charting. Care of eyes involves frequent use of eye lubricants and avoidance of exposure keratitis. Strict asepsis is needed to avoid infections and the use of broad-spectrum antibiotics whenever required is essential.

A multidisciplinary team approach inclusive of ophthalmologist, orthopedician, geneticist, dietician, occupational therapist, and physiotherapist is required for effective management of case [4,9]. Drug treatment involves systemic use of retinoids which causes rapid shedding of hyperkeratotic skin plates within the first few weeks. Etretinate was initially used, now acitretin is a widely used retinoid, which is started in the early neonatal period [9,13]. Detailed prenatal genetic counseling is very crucial for future pregnancies. Newer DNA-based molecular techniques and advanced radio imaging techniques enable early diagnosis of HI. Knowledge of the exact mutations will assist in the development of allele-specific therapies within the era of personalized medicine for these rare heritable disorders [14].

CONCLUSION

HI is a very rare genodermatosis which requires significant attention in the neonatal period. It can be successfully managed by multidisciplinary approach. Simple measures, including daily bathing and liberal use of emollients, serve as mainstays of treatment, in addition to newer retinoids drugs like acitretin.

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