

# Ichthyosis congenita, harlequin fetus type: a case report

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## ABSTRACT

Ichthyosis is a very heterogeneous family of skin disorders with harlequin ichthyosis being the most severe genetic form. It is a rare autosomal recessive condition, characterized by dry, severely thickened skin with large plates of hyperkeratotic scale, separated by deep fissures. Infants are very susceptible to metabolic abnormalities and infections. They usually do not survive for very long, but several long term survivals have been noted. The vast majority of affected individuals are homozygous for mutations in the ABCA12 gene, which cause a deficiency of the epidermal lipid transporter, resulting in hyperkeratosis and abnormal barrier function. We report a case of a newborn with harlequin ichthyosis, born to unrelated parents, who had a favorable evolution with topical treatment and intensive care.

**Key words:** harlequin ichthyosis, hereditary, ABCA12 gene mutations, new case

## INTRODUCTION

Ichthyosis is a very heterogeneous family of skin disorders, harlequin ichthyosis (OMIM #242500) being the most severe genetic form. At birth, the skin is very hard and thick, forming a dense "armor"-like scale that covers almost all parts of the body. The skin forms large diamond- or triangular-shaped plates separated by deep fissures. The protective skin barrier is compromised and the infant is very susceptible to infections. These skin abnormalities also affect the shape of the eyelids, nose, mouth, and ears. A restriction of movement of the arms and legs is present. Breathing difficulties and respiratory failure may also occur, probably due to pulmonary surfactant deficiency, caused by mutations in the ABCA12 gene.

Studies performed in order to investigate the pathomechanism of harlequin ichthyosis and the function of the ABCA12 protein revealed that lung alveolar collapse may occur immediately after birth. Reduction in the level of surfactant protein B, an essential component of alveolar surfactant, was noticed [1]. The affected neonate is usually of low birth weight for dates. This condition is often lethal in the neonatal period, but with intensive care and the use of drugs, lifespan has been prolonged. The disorder has an autosomal recessive inheritance. The vast majority of individuals with

harlequin ichthyosis have been found to be homozygous for mutations in the ABCA12 gene. The ABCA12 (adenosine triphosphate [ATP]-binding cassette transporter, subfamily A, member 12) gene was mapped to chromosome 2q33-q35. The normal gene has 53 exons and encodes a protein that belongs to a subfamily of ATP-binding cassette transporters and is responsible for the transport of epidermal lipids and their processing enzymes in and out of specialized organelles in the upper layers of the epidermis. More than 30 different mutations of the ABCA12 gene have been identified in individuals with harlequin ichthyosis. Most are nonsense mutations and small insertions/deletions that result in premature termination of protein translation. Partial gene deletions, spanning from one to more than 30 exons, have also been found.

The consequence of the mutation is represented by a deficiency of the epidermal lipid transporter. These changes prevent the formation of lipid bilayers in the stratum corneum and result in hyperkeratosis and abnormal barrier function [2]. Harlequin type congenital ichthyosis was subdivided into 3 subtypes. In types 1 and 2, profilaggrin is expressed but not processed to filaggrin, whereas type 3 lacks profilaggrin. Profilaggrin is the major protein of keratohyalin granules in the epidermis. During terminal differentiation, it will be cleaved into multiple filaggrin peptides that aggregate keratin filaments.

**Figure 1.** Clinical features of the face of the proband 4 days after birth.



Profilaggrin accumulates in keratohyalin granules and undergoes dephosphorylation and proteolysis to filaggrin [3,4]. A defect of conversion of profilaggrin to filaggrin was suggested as a possible pathogenetic mechanism as protein phosphatase is thought to be involved both in the conversion of profilaggrin to filaggrin and in the synthesis of the lipid content of lamellar granules [5].

## CASE REPORT

A 3 day-old female newborn was referred to our Medical Genetics Department. The subject was born to a healthy 30-year-old mother, gesta I, para I and her 24-year-old husband, both with no relevant medical history. The pregnancy was not monitored, as the parents live in a village, far from a medical care unit. The pregnancy was complicated by oligohydramnios. Rupture of the membranes had occurred 3 days before birth.

The infant was born by vaginal delivery. The Apgar score was 7. The birth parameters were: weight 2430 g, length 42 cm, head circumference 31 cm, and thoracic circumference 28 cm. The clinical aspect of the infant was unusual. Physical examination revealed that the skin was thickened, hard, with yellowish and leathery white regions, split irregularly by deep erythematous fissures. The infant also had ectropion, rudimentary ears, nasal hypoplasia, eclabium and fixed, open mouth (Fig. 1). Fingers and toes were hypoplastic. The limbs were in a semiflexed position, with flexion contractures at elbows and knees and limited mobility (Fig. 2; Fig. 3). External genitalia were female.

She was not able to suck because of the mouth abnormalities. Parenteral route for nutrition was used. Ultrasonography of the abdomen did not reveal any abnormality. The newborn was placed in a humidified incubator and a sterile environment was maintained to avoid infections. Treatment was initiated with sterile olive oil and emollient creams to soften the skin. Local antiseptics were also applied. Ectropion was covered with

**Figure 2.** General aspect of the proband with severe hyperkeratosis, fissures and with flexion contractures at the elbows and knees at birth.



**Figure 3.** General aspect of the proband with severe hyperkeratosis, fissures and with flexion contractures at the elbows and knees 4 days after birth.



eye pads soaked in saline solution and ophthalmic ointments were also used. Oral retinoid therapy was not used, because of the lack of experience with these drugs and also due to the favorable evolution with the topical treatment during the three weeks of hospitalization. Regular physical examination was recommended, but further data were not available, as parents did not return to the clinic.

## DISCUSSION

Harlequin fetus is a rare hereditary disorder with an incidence of 1 in 300 000 births. The first report was made by Reverend Oliver Hart, of Charleston, South Carolina, who described some features of the disorder in 1750 [6]. Until now, at least 100 cases were reported with this condition. The disorder was reported in different ethnic groups and in both sexes. The inheritance is thought to be autosomal recessive, supported by consanguinity in some families with affected offspring. There was no consanguinity in our case.

For a long time, the pathomechanisms and the underlying genetic defects of the disease were not known. ABCA12 mutations were then reported as the main cause of the disease [2, 7]. Affected individuals are usually homozygous for the mutation, consistent with the autosomal recessive pattern of inheritance. ABCA12 belongs to a large superfamily of ABC transporters, which bind adenosine triphosphate while aiding the transport of different molecules across the cell membrane. Members of the ABCA subfamily are all involved in lipid transport. The ABCA12 gene has the genetic information for a transmembrane protein that mediates lipid transport, essential to the transfer of lipids from the cytosol of the corneocyte into lamellar granules. Most ABCA12 mutations lead to severe truncations and seriously affect ABCA12 peptide function [8].

Affected infants usually do not survive for very long because of undernourishment caused by the rigidity of the lips, underventilation and infections, but longer survival was also reported. Experimental studies using model mice reproduced the human skin phenotype and provided further evidence that ABCA12 plays an essential role in lung and skin barrier functions [1]. Treatment of congenital ichthyosis uses oral vitamin A, topical antiseptics, liquid paraffin, five percent lactic acid lotions [9]. Oral retinoid therapy is recommended for cases with severe skin involvement. Potential adverse effects, such as impairment of liver function, growth retardation or remaining erythroderma must be taken into consideration and discussed with the parents.

Prevention of secondary complications is also important. Several measures, such as the prevention of infection and of dehydration, together with maintenance of body temperature are appropriate. Creams or ointments are used to keep the skin soft and hydrated, keratolytic agents will promote peeling and thinning of the stratum corneum. Lubrication of the cornea in cases with ectropion prevents corneal drying. Weight gain and fluid intake must be carefully monitored. A multidisciplinary approach is vital in the management of the disease as it could prolong survival beyond the neonatal period.

Prognosis depends on possible complications. The survival rate of children born with this condition has improved over the years, but still the most common cause of death remains fulminant sepsis. After discharging from the hospital, the primary care physician should closely monitor the infants for growth, skin surveillance and development. Parents of affected

children also need support. There is no report about a similar case in our country. As far as we know, this is the first baby born with this form of ichthyosis in Romania.

## CONCLUSIONS

Our patient had the typical phenotypic features of a harlequin fetus. Harlequin ichthyosis is the most severe form of congenital ichthyosis. This condition is inherited in an autosomal recessive pattern. The vast majority of affected individuals have been found to be homozygous for mutations in the ABCA12 gene that was mapped to chromosome 2q33-q35. Infants usually do not survive for long, but our case had a favorable evolution with intensive care, topical treatment and prevention of secondary complications. Management of patients with harlequin ichthyosis requires a well coordinated multi-disciplinary approach.

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