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Case report

New variants of *ABCA12* in harlequin ichthyosis baby

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Abstract

Harlequin ichthyosis (HI) is an extremely rare genetic skin disorder and the most severe form of a group of disorders, which includes lamellar ichthyosis and congenital ichthyosiform erythroderma. It consists in an autosomal recessive disorder with the majority of affected individuals being homozygous for mutation in the *ABCA12* gene. This condition presents a wide range of severity and symptoms. Affected neonates often do not survive beyond the first few days of life and it was usually considered as being fatal in the past, but, with the improvement of neonatal intensive care, the survival of these patients also improved.

Our report is about a harlequin baby with new variants, which have not been previously described. He presents two variants in heterozygosity in the *ABCA12* gene: c.3067del (p.Tyr1023Ilefs * 22) and c.318-2A>G p(.?), inherited from the father and mother.

Several aspects concerning genetics, physiopathology, diagnosis, treatment and prognosis are discussed. An intensive neonatal care and early introduction of oral retinoids improve survival rates in this kind of disorder.

Keywords

Clinical genetics, dermatology, genetics, harlequin ichthyosis.

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Introduction

Harlequin ichthyosis (HI), reported for the first time in 1750 by Reverend Oliver Hart [1], is a severe disorder of the keratinization process caused by loss of function due to mutations in *ABCA12* gene. ABCA12 (an ATP-binding cassette [ABC] transporter) forms a large superfamily of transporters that bind and hydrolyze ATP to transport various molecules across limiting membranes or into vesicles. ABCA12 is a keratinocyte transmembrane lipid transporter protein associated with the transport of lipids via lamellar granules during the formation of the lipid barrier, which is essential for skin barrier function [2]. *ABCA12* mutations lead to ichthyosis phenotypes from malformation of the stratum corneum lipid barrier.

HI is a rare disease with an incidence of approximately 1 in 300,000 births, slightly higher in Norway (1:91,000) and in Galicia (1:122,000) as a result of a founder effect [3, 4]. The disease affects all ethnic groups and is associated with substantial morbidity and mortality [5]. Previous reports have shown that many babies die soon after birth, but with the development of early-onset postnatal care, greater awareness of the condition, improved quality of care and possibly early treatment with oral retinoids have been achieved. In most recent series, the survival rate is higher than 50% and more than half of the deaths occurred in the first 3 days of life [6].

We report a case of harlequin baby, which reflects the actual good evolution of a severe case hospitalized in a neonatal intensive care unit (NICU). Early diagnosis with appropriate treatment options associated with a multidisciplinary team can reduce the mortality of the disease and improve the prognosis of these children in the long term.

Report of a case

The patient was a male newborn born at 34 weeks of gestation admitted to the NICU with thick, fissured armor-plate hyperkeratosis of the skin, severe ectropion (eversion of the eyelids), eclabium (eversion of the lips) and malformation of the auricle (**Fig. 1**). He was born by vaginal delivery with 2,440 g of weight, 46 cm of stature and 33.8 cm of head circumference. Apgar scores at the 1st and 5th minutes were 9 and 10, respectively. The mother had an uncomplicated and medically supervised pregnancy up to 29 weeks, when prenatal ultrasound revealed a foetus with persistently open mouth, closed hands and reduced foetal movements. Subsequent ultrasound showed tongue protrusion, plantar oedema, and short fingers. The prenatal investigation excluded the most common aneuploidies and the changes found in the array-CGH were nonspecific. His parents were 30 and 34 years old, were healthy and non consanguineous. No similar pathology was reported in their families and they had a healthy 5-year-old first daughter.

On arrival to NICU, the newborn was spontaneously breathing and hemodynamically stable. After dermatological consultation, topical emollients were regularly applied on the skin, from the first day of life, with progressive improvement of the skin aspect. Detachment of the hyperkeratotic plaques in a large part of body was obtained on discharge. Although laboratory tests did not show any infection, antibiotic therapy with intravenous ampicillin and gentamicin was started as prophylaxis of secondary infections. On the 3rd day of life, the administration of 1 mg/kg/day of acitretin was started. Because of the intense pain, in the first day, he underwent morphine infusion, which was suspended for the development of apnoea. The pain was then controlled with paracetamol up to day 8, with progressive improvement allowing analgesia suspension. It was performed the disease exome (TruSight One Sequencing Panel) that identified two variants in heterozygosity by father and mother, in the *ABCA12* gene, probably of pathogenic nature: c.3067del (p.Tyr1023Ilefs * 22) and c.318-2A>G (p.?), which are not described in the literature nor in population databases.

The patient was discharged after 40 days of hospitalization with good general condition (**Fig. 2**). He was breastfed well and growing properly. There was limitation of hip abduction bilaterally and he maintained light ectropion and hyperkeratosis. A multidisciplinary team in consultations of general pediatrics, dermatology, otorhinolaryngology, ophthalmology and orthopedics followed him. Clinical improvement in the infant's condition was seen over the subsequent weeks. He is currently 9 months old (**Fig. 3**). He is followed at Pediatric

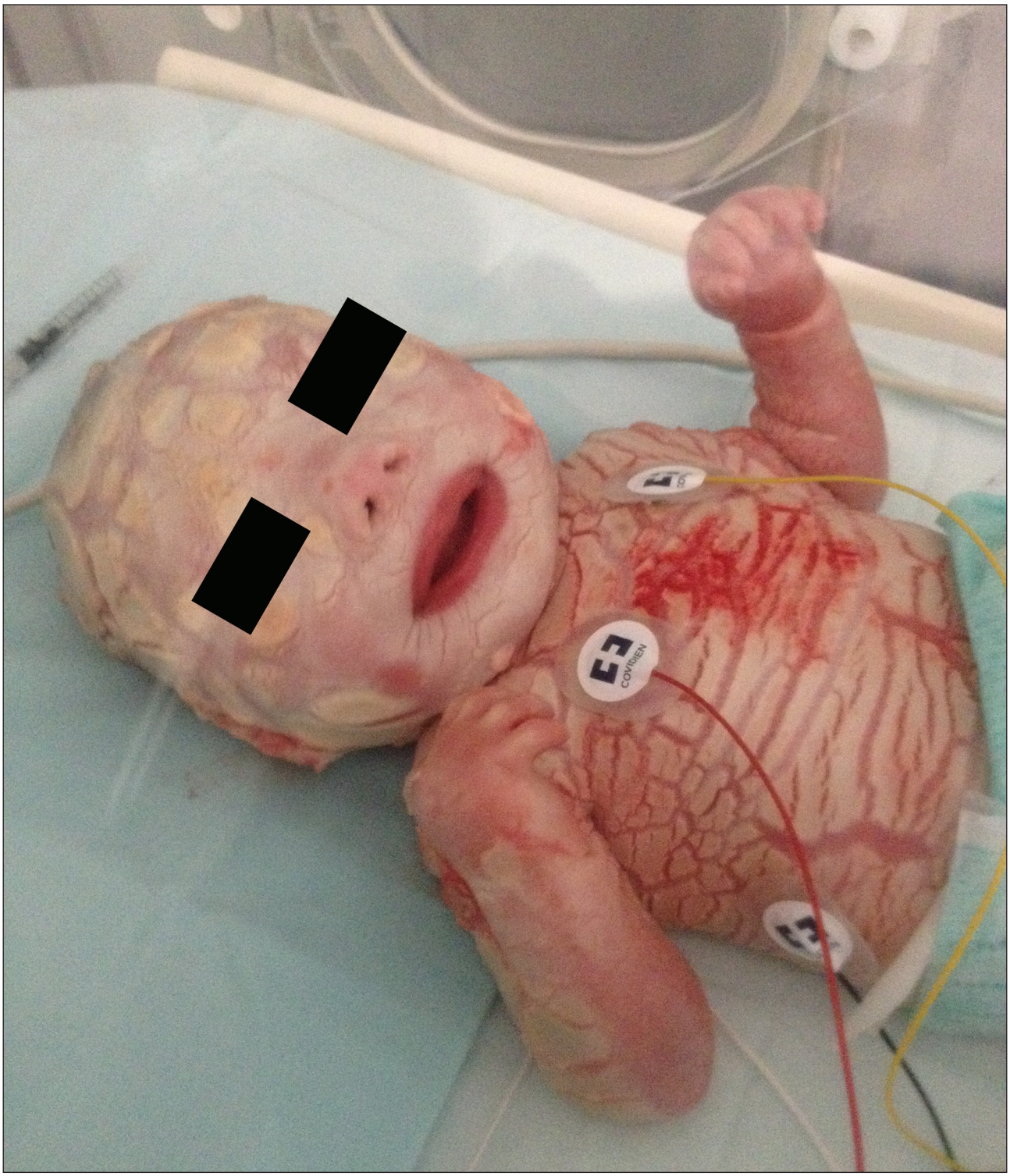

Figure 1. The neonate with harlequin ichthyosis on day 1 of life.

Hospital of Coimbra showing weight in the 3rd percentile in the WHO weight-for-age charts for adjusted age and good growth. Nostrils have no obstruction, auricular pavilions are formed with some deformity, and external auditory canals (EAC) are obstructed by hyperkeratotic plaques. He reacts to sounds. He maintains light bilateral ectropion but presents full eyelid closure. Hands are predominantly closed with thumbs on the palm and right thumb with some hypoplasia. He has right interphalangeal hallux varus and limitation of hip abduction. He shows a normal development for his age. Topical emollients are regularly applied for intensive hydration and he is on systemic treatment with acitretin, with serum lipids and liver function tests being performed regularly.

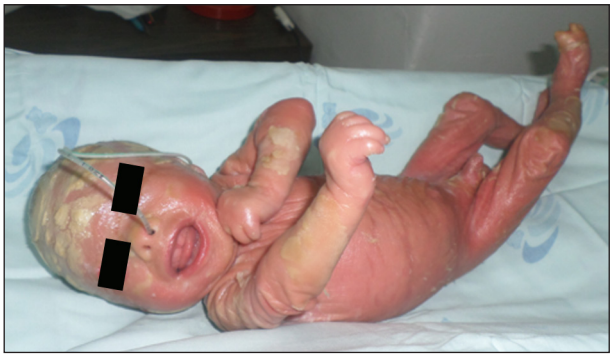

Figure 2. The baby on discharge after 40 days of hospitalization and treatment with acitretin.

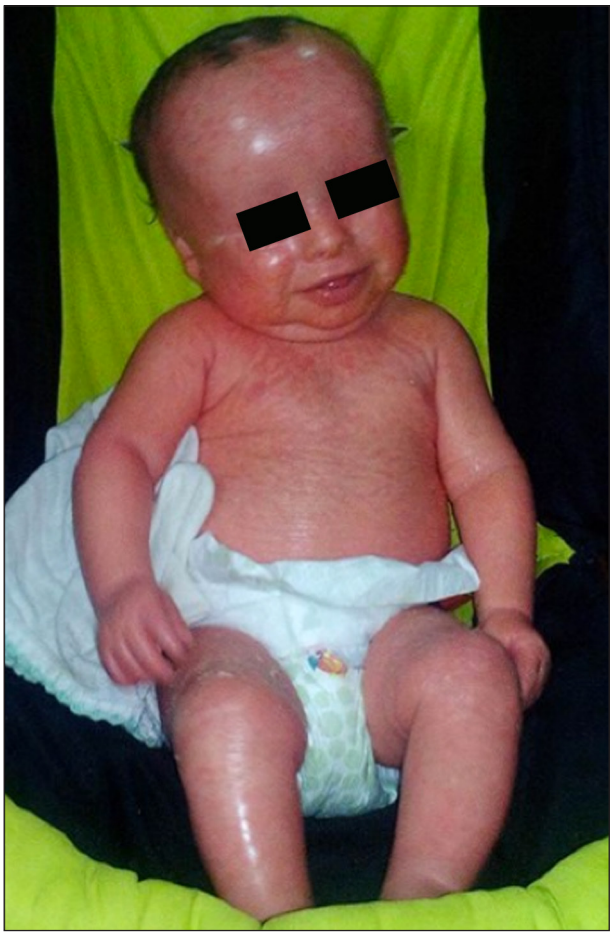

Figure 3. The baby at present time, at age of 9 months.

Discussion

Harlequin ichthyosis is a rare disease associated with substantial morbidity and mortality. The introduction of oral retinoids, as soon as possible after birth, and a more active management approach overall probably improves survival. It is the most severe type of ichthyosis and survivors will have a lifelong skin disease, although the mechanism behind this phenotypic recovery remains unclear. Mutation analysis should be offered to all women with previously affected babies with known familiar mutation. In this case, risk of this couple having affected offspring is 25% at each gestation, for this reason, specific prenatal diagnosis is recommended in future pregnancies. Common features of the disease can be recognized through ultrasounds but tend to appear lately. Ultrasound can reveal abnormal facial features like ectropion, eclabium, short foot length, incurved toes, clenched fists, poor delineation of nostrils, and polyhydramnios [7]. In our case, the absence of a family history, associated with the late onset of the changes in the foetal ultrasound, made the prenatal diagnosis difficult, leading to a diagnosis only after birth.

HI presents at birth and is clinically diagnosed. Neonates born with HI with mean gestational age at birth of 35 weeks (range 30-39) [5] have a typical appearance of generalized, thick, yellowish, hyperkeratotic plates with deep erythematous fissures, particularly on the trunk as described in our case (**Fig. 1**). Skin biopsy is no longer used to diagnose the disease [5]. Although it is a rare condition, improved neonatal care has increased survival [8, 9]. Treatment and supportive care is required throughout the patient's life to address complex needs and involves a multidisciplinary team of pediatricians, dermatologists, ophthalmologists, otolaryngologists, plastic surgeons, psychologists, dieticians and geneticists. In the neonatal period, patients need to be sent immediately to a NICU to prevent complications such as respiratory distress, dehydration, electrolyte imbalance (hypernatremia, hypocalcemia, and hypoglycemia), impaired thermoregulation, systemic bacterial infections and feeding difficulties. The patients are placed in a humidified incubator to maintain heat and given supportive intravenous fluids to avoid dehydration. It is important to keep invasive procedures to a minimum and to be vigilant for signs of sepsis and avoid skin infection. In our case, the use of invasive devices and procedures that would increase the risk of infection and associated morbidity was as minimal as possible. Our patient was always kept in spontaneous breathing and the umbilical venous catheter was only maintained during antibiotic prophylaxis. Some authors support that prophylactic antibiotics should be used to prevent sepsis, but there are only a few studies focused on the benefits of antibiotic or fungal prevention in patients with HI, and there are cases of HI patients who died from septic shock despite the use of

broad-spectrum antibiotic [10]. Review of the mortality data shows that respiratory failure causes death as commonly as sepsis. This may simply arise because the thickened skin restricts chest wall movements or makes breathing too painful, resulting in poor pulmonary ventilation. Opiate analgesia is given in the neonatal period to relieve this pain but may cause respiratory depression itself, as occurred in the described case. Topical emollients should be applied regularly to the skin. Current systemic treatment usually includes acitretin, an oral retinoid that has widely replaced its parent compound etretinate in the treatment of disorders of keratinization because of its shorter half-life. It has been suggested that patients treated early with acitretin may have a survival advantage [5, 6]. Systemic retinoids can be used early in life to hasten this shift in clinical presentation and may lead to a decrease in mortality, as they encourage keratolysis, keratinocyte differentiation, and shedding of the thick hyperkeratotic encasing. They may also have an anti-inflammatory effect related to the drugs' ability to modulate neutrophil activation and function [10].

Concerning genetics, mortality was frequently associated with homozygous mutations. Some studies show that some babies with compound heterozygous mutations also die, but these are the minority. The coexistence of other serious recessive diseases may be one explanation. However, the nature of the *ABCA12* variants may also affect the severity of the disease. Akiyama et al. described a patient with HI of moderate clinical severity who presented a maternal deletion mutation of a highly-conserved residue in exon 28 and a *de novo* missense mutation in exon 10, that corresponded to the first nucleotide-binding fold and cytoplasmic domain, respectively [11]. They raised the question that, while the missense mutation was unexpected to significantly change the protein's function, when added to the deletion mutation, the HI phenotype still exists but with a milder clinical severity in similarity to what happens in the case presented [11]. In these cases, the variants are in heterozygosity and are probably of pathogenic nature. The study of the father identified a variant c.3067del (p.Tyr1023Ilefs * 22) in heterozygosity which was not described in the literature neither in population databases, which due to its nature – a frame shift change – is supposed to introduce a stop codon premature, leading to the production of a truncated ABCA12 protein and/or the loss of expression by degradation of messenger RNA. Thus, it is classified as a pathogenic variant. The study of the mother identified the c.318-2A>G (p.?) variant, also not previously described in literature, which is located at the splicing acceptor site of intron 3, so the skipping of exon 4 is very likely. This variant should then be classified as pathogenic. Together, the results of both parents allowed us to conclude that variants of the *ABCA12* gene detected in the child are found in different alleles (trans), which leads to the association of the two mutations resulting in the completely abnormal functioning of the protein. Mutation analysis is especially relevant if preimplantation or early prenatal diagnosis is considered during the first trimester of pregnancy. The history of the familiar mutation can provide an earlier diagnosis by amniocentesis or chorionic villous biopsy or *in vitro* fertilization, which may lead to a preimplantation diagnosis.

Patients who survive the neonatal period will live with a chronic skin disease that needs to be managed on a daily basis with the frequent use of topical emollients and, sometimes, intermittent use of oral acitretin. Vitamin D deficiency can cause rickets and, in these patients, monitoring of vitamin D levels and providing supplements is essential because sun exposure may be limited [6]. Surgical correction may be required for persistent ectropion, but recurrence is frequent. To avoid corneal drying, the use of artificial tears for lubrication of the cornea is helpful. Infants and children can develop hearing difficulties caused by blockage of the external auditory canal from skin debris, which requires regular ear microsuction. Although there is some delay in achieving developmental milestones, many children are able to attend a mainstream school with appropriate support and adults can enter higher education and live independently. However, in some cases the frequent hospital admissions can interrupt development of their speech, language, and social skills. Speech and language therapy input may be beneficial. It is important not to forget that, as with any dermatologic disease, support from a psychologist may help those who feel self-conscious about their appearance.

Conclusions

In conclusion, we describe a rare case of a serious and complex illness, with a novel mutation, which has not been previously described, where early

and appropriate treatment is a major challenge and depends on the commitment of a multidisciplinary team to achieve a non-fatal ending.

Declaration of interest

The Authors declare that there is no conflict of interest.

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