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Review Article

Harlequin Syndrome Report of a Case: Prenatal Diagnosis and Neonatal Approach

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Abstract

Harlequin ichthyosis is a pathology of autosomal recessive origin which occurs at birth, it is shown with intense hyperkeratosis with thick fissures, causing high skin tension in the periphery of the eyes, ears, mouth, abdomen and extremities; erythroderma due to increased skin permeability, which leads to greater loss of transepidermal water. They can also present extra-cutaneous manifestations such as hearing impairment, short stature, eye disease, low intellectual capacity. Within the management, special care must be taken with the protection of the skin, with adequate cleaning, hydration using emollients and moisturizers as well as retinoids that reduce skin thickening and flaking, without modifying the erythema or inflammation, in addition, antibody therapy has been used emollients and moisturizers as well as retinoids that reduce skin thickening and flaking, without modifying the erythema or inflammation, in addition, antibody therapy has been used recently omalizumab and infliximab-like monoclonal drugs and corticosteroid pulses. In our article we report the almost prenatal diagnosis with subsequent follow-up in the first days of life.

Keywords: *Autosomal Recessive; Hyperkeratosis; Ichthyosis; Ultrasound Markers; Cardiomyopathy; Hydroelectrolytic Imbalance*

Introduction

Congenital ichthyosis

Congenital ichthyosis is a rare disorder, with autosomal recessive transmission, characterized by hyperkeratosis throughout the skin with dyskeratosis, peeling, inflammation, erythroderma due to increased skin permeability, which leads to greater loss of trans-epidermal water. Ichthyosis vulgaris being the most frequent form and Harlequin ichthyosis the most severe [1].

Epidemiology

Few details have been reported on the epidemiology of patients suffering from congenital ichthyosis syndrome, since its incidence is generally low, so the clinic and treatment are incompletely reported. However, studies have shown the predominance in men, with a male: female ratio from 0.83: 1 to 3:1 depending on the type of congenital ichthyosis presented and the age of diagnosis [2].

Ichthyosis vulgaris is the most frequent ichthyosis, with an approximate incidence of between 1: 250 to 1: 1000.1, its manifestations begin at 2 months of age, generally affecting the back and legs.

X-linked recessive ichthyosis has a prevalence of 1:2,000 to 1:600,014. The reported mortality rate ranged from 1.7% to 5.6% in congenital ichthyosis; and from 25% to 50% in harlequin ichthyosis with death generally in the first 72 hours of life, generally related to respiratory failure and severe hydroelectrolytic imbalance [2,15,17,20].

Classification

There are different types, such as non-syndromic ichthyosis in which the phenotypic disorder is only visible on the skin, these include ichthyosis vulgaris, X-linked recessive ichthyosis, autosomal recessive congenital ichthyosis, keratinopathic ichthyosis and autosomal recessive congenital ichthyosis syndromes, which include harlequin ichthyosis, lamellar ichthyosis and erythroderma with congenital ichthyosiform, plus three of the subtypes minor: baby self-healing collodion (less severe form where peeling resolves almost completely during the first 3 months of life), self-healing collodion acral (which peels 3 - 4 weeks after birth) and suit ichthyosis bathroom (they present scaling without erythema on the trunk, proximal area of the thoracic limbs, scalp and neck, generalized scaling but without erythema [2,14,17].

Harlequin ichthyosis (HI) is the most severe phenotype of congenital ichthyosis. It is characterized by severe ectropion, eversion of the lips and flattening of the nasal and ear cartilage, in addition to skin alteration as a barrier, coupled with hypernatremic dehydration and alteration of body temperature, with increased metabolism and a higher incidence respiratory failure and sepsis [13,18,20,21].

Pathophysiology

They have been identified in the ABCA12 gene on chromosome 2, chromosome 12p11.2-q13 and some frequent mutations that are related to autosomal recessive congenital ichthyosis, such as in acylceramide-associated genes (a long-chain sphingoid base compound and a fatty acid that binds to the amide, with different number of carbons in its chain, as well as degree of unsaturation and hydroxylation position) the KDSR (3-ketodihydrophosphosine reductase) and ELOVL4, the functional alteration transporter of binding cassette to adenosine triphosphate encoded with leads to inadequate transport of lipids within the keratinocytes, likewise there are reports of subtypes of alterations in congenital ichthyosis, based on dysfunction of the following 14 genes: TGM1, ALOXE3, ALOX12B, ABCA12, NIPAL4, CYP4F22, PNPLA1, CERS3, LIPN, SDR9C7, SLC27A4, ST14, SULT2B1 and CASP14, which mostly alter lipid metabolism in the cornification period, which alters the lipid envelope [3-6,9,11-13,15,21]. The ABCA12 gene is formed by essential gene proteins, with specific trans-

porters of the plasma membrane and intracellular compartments, the function of transporter whose function is to facilitate the supply of lipid glucosylceramides in lamellar granules of the epidermis, which later they move to the extracellular space, therefore, the skin presents compensatory extreme hyperkeratosis, its function as a barrier being damaged. Mutations have also been found in proteins such as SDR9C7, which is overexpressed in granular and cornified layers of the epidermis, as well as truncation mutations, nonsense mutations, exon deletions, and single amino acid deletions [3,9,11,13, 20,21].

The SDR9C7 protein (formerly SDR-O), a member of the SDRSe family of enzymes, which catalyzes the activation/inactivation of prostaglandins, retinoids and steroid hormones, is involved in the metabolism of vitamin A. It has been associated with interleukin 17 and interleukin 22 as well as the presence of T helper type 17 with skin alterations in ichthyosis, which may present resemblance to psoriasis, increasing the degree of severity and trans-epidermal water loss, the relationship has been reported mRNA expression of proinflammatory cytokines and chemokines based on the severity of ichthyosis, showing patterns of mRNA expression in 54 genes which encode proteins necessary for the skin barrier [8,11].

Among the alterations described in the disease, dysfunction of the lipid envelope of the corneocyte is reported, preventing its transformation into lamellar membranes, leaving the extracellular laminae exposed in the epidermis. The presence of epidermal hyperplasia has been reported, finding inclusions in ichthyosis lesions such as dendritic cells, CD3, CD11 neutrophils, in the infiltrates, being similar to those found in patients with psoriasis, however, there is a predominance of Th17 infiltrates. Mutation in the gene that encodes profilaggrin, filaggrin precursor protein, was recently established as the cause of ichthyosis vulgaris, affecting the protective barrier [1,7,14].

Specifically within the alterations in congenital ichthyosis of the Harlequin ichthyosis type, there are few evident changes in the basal, spinous and granular layers, with little or no inflammatory cell infiltration; absence of lamellar granules, altered multivesicular bodies, autolysosomes in the cytoplasm of the keratinocytes of the upper spinous layers and in the granular layers, with few giant mitochondria within the keratinocytes with a predominance of the scalp, face, trunk and extremities; except for the tongue [20,21].

Clinical picture

In congenital ichthyosis there is a variety of clinical manifestations from hearing problems, short stature, eye disease, low intellectual capacity, alterations in hair follicles and short limbs, it can present severe hypo or anhidrosis increasing the risk of hyperthermia, in addition to the fact that they can show pictures of pneumonia due to aspiration of the residues due to detachment in the amniotic liquid [2,18,19].

Despite knowing that the inflammation, thickening of the skin and the presence of scaling are due to the skin barrier disorder, few investigations have been carried out on the molecular basis of these phenotypic traits. They can present necrosis in extremities as well as limitation of movement due to hyperkeratotic bands, it also increases the rate of neonatal morbidity and mortality, causing a high risk of secondary infections such as mycosis, temperature changes, increased water loss through the epidermis, delay in starting feeding as well as difficulties-respiratory rate [3,8,11,18].

In childhood, recurrent skin infections, alopecia, delayed growth and development, short stature, arthritis, nail dystrophy, scarring alopecia are common. Ophthalmic alterations, among the most frequent presented in 64% persistent ectropion, in 48% there was epiphora and up to 12% keratitis due to exposure, in addition, scarring and corneal perforation have been reported, as well as cataracts due to the use of corticosteroids and retinoids, with a higher risk of developing skin cancer [3,18,21,22].

Harlequin ichthyosis (HI) is the most severe form that exists, occasionally it is fatal, they present thick scales in the form of plates with severe ectropion, ectropion and flattening of the ears, the skin condition begins from the uterus, the hyperkeratosis of the hair fol-

licle begins in the second trimester and alterations structural as altered lamellar granules that are seen in the affected fetal epidermis [14,17,18,21].

Diagnosis

Harlequin ichthyosis is generally diagnosed at birth due to its phenotypic characteristics, but up to 60% of patients may require histopathological study, genetic studies, with the identification of the altered locus in Harlequin ichthyosis, on chromosome 2q25, evidencing premature termination, insertion, deletion as well as frameshift mutations, concluding in an absent or truncated ABCA12 protein, which influences the severity of clinical presentation [2,13,14,20].

Genetic diagnosis can be carried out after birth, this, in addition to allowing diagnosis, helps to determine the prognosis and based on this, adequate genetic counseling can be given to parents; it has been reported that the prevalence of genetic alterations in neonates is up to 9%, of these less than 10% have been diagnosed prenatally, which encourages patients with data suggestive of genetic alteration have longer stays in the NICU for management and genetic diagnosis [10,13].

Prenatal diagnosis

Previously, fetal skin biopsy was performed by electron microscopy, however this invasive technique has been replaced by the determination of fetal DNA in amniotic fluid obtained through ultrasound-guided amniocentesis, as well as villus biopsy. Does chorion, the determination of mutations in AB-CA12 has also been reported, which can also be performed in fetal hair by means of r-messenger RNA [13,14].

Prenatal ultrasound

Identification of signs suggestive of harlequin ichthyosis, such signs as eclabium (eversion of the lips), ectropion, rudimentary ears, presence of cysts near the eyes, thickening of the skin, fetal hypomobility, rigidity and hypoplasia of the extremities, which are semiflexed, hypoplasia of fingers and toes, as well as clubfoot, the amniotic fluid can be visualized hyperechoic, contractures which will limit fetal movement, also in the amniotic fluid hyperechoic floating particles "sign of Snowflake".

Treatment

Within the experimental prenatal therapies, the intra-amniotic injection of retinoids and steroids has been tested in mice, without achieving any benefit or improvement in prognosis to date [3,20]. At birth, the most important thing is an adequate neonatal resuscitation in expert hands due to the co-morbidities that these patients present and in a hospital unit that includes a multidisciplinary team: neonatology, dermatology, genetics, ophthalmology, otorhinolaryngology, orthopedic and plastic surgery, nutrition, physiotherapy and nursing, the vast majority of these patients require airway management due to the high risk of respiratory failure with catastrophic results, as well as increased metabolism, loss of regulation of temperature, hydro-electrolyte imbalance, so electrolytes must be constantly monitored, in addition to maintaining nutrition, pain control due to deep fissure injuries that can affect the epidermis, as well as prophylaxis by cons-high risk of secondary infections, the most common being infections by *Staphylococcus aureus*, dermatophytes and *Candida*, however they occur infrequently [1,13,17,18,20].

Special care must be taken with the protection of the skin, performing adequate cleaning as required, up to twice a day, maintaining adequate hydration, 0.125% sodium hypochlorite mixed 1:10 with hot sterile water has been used, the optimum pH is 8 to 8.5, applied with gauze and wrapped in plastic for a period of 10 to 20 minutes, in addition to using emollients after removing the gauze. Other mois-

turizers such as vaseline, virgin coconut oil and sunflower seed oil have also been used, with favorable results. Retinoids have also been used, which generally improve, but in some cases can increase inflammation, in addition to it only decreases the thickness of the skin and desquamation, without modifying the erythema or inflammation, likewise its side effects such as teratogenicity, hypertriglyceridemia and hyperostosis, cheilitis, itching, hair loss and epistaxis, make its use limited, it is suggested to avoid the application of keratolytics in neonates such as salicylic acid, urea, lactic acid and propylene glycol despite reducing the adhesion of keratinocytes. They can cause toxicity; as a surgical treatment, fasciotomy of the phalanges and/or extremities can be performed to manage compartment syndrome, avoiding progression to necrosis due to epithelial compression. Eyelid surgery has been used in ectropion with skin graft for ocular alterations, with the aim of preserving the cornea.

Recently, treatment with monoclonal antibodies such as omalizumab and infliximab accompanied by corticosteroid pulses in the first month has been used in patients with expression of ichthyosis, with an adequate clinical response, reducing blood levels of ichthyosis by more than 50%. IL-1b, IL-5 and IL-17, Likewise, the role of Th17/IL-23 and its bias in terms of the alteration of the skin as a barrier has been elucidated, finding repercussion and the association of IL markers-17 and IL-17/TNF modulators with severe forms and inflammation of the disease, for which improvement was shown with a decrease in IL-17 after the use of infliximab (anti-TNFα), giving a new expectation in terms of evidence-based treatment of ichthyosis.

Aftercare

The altered keratotic epithelium that presents at birth in harlequin ichthyosis, presents transformation in a period of 4 - 6 weeks due to an extreme ichthyosiform erythroderma due to the dry environment, so it is important to care for the skin with care. Emollients, although they present less risk of infection than in the neonatal period, care should not be omitted, considering that they may also have intolerance to cold and heat. In addition, when there is persistence of ectropion, it must have eye protection and lubrication [13].

Physiotherapy and occupational therapy have been put into practice in childhood to improve body motility, likewise, some babies and children have presented cognitive deterioration, for which speech therapy is considered necessary [13].

Ethical importance

The moment of diagnosis of a baby with Harlequin ichthyosis can be shocking for both parents and health workers, due to the surprising physical appearance of the newborn with IH, it can lead to the appreciation of meriting low quality of treatment and greater treatment. Body pain, so medical attention is important. Currently, infants with IH have a similar survival rate and more favorable neurocognitive outcome than, for example, infants born at 26 weeks' gestation, a situation in which aggressive intervention is usually initiated when available. At the same time, it must be recognized that more difficult ethical scenarios may arise; for example, HI patients with additional or complicated medical problems, settings without resources for intensive care or long-term medical treatment. Consideration of comfort care over intensive care management might be appropriate in such selected situations.

Case Report

Report of a clinical case, in the Morelos women's hospital.

A case of a newborn patient is reported, fourth in order of birth, parents with no relevant history, no consanguinity, birth due to delivery at 29.3 weeks of gestation. Mother admitted due to anhydramnios, requesting evaluation by maternal-fetal medicine, with evidence of anhydramnios and a live fetus, with fetometry 23.5sdg, weight 767gr +- 97fr percentile (P.) < 3, FHR 144/min, altered flowmetry by IP umbilical artery 1.56, P. > 95, middle cerebral artery pulsatility index 1.44 percentile < 5, cerebroplacental index 1.098 P. < 5, IP mean uter-

ine arteries 0.75 P. < 95; evidence of cardiac remodeling, with probable hypertrophic cardiomyopathy, pericardial effusion, cardiomegaly, secondary pulmonary hypoplasia, nasal bone hypoplasia (3 mm), prenatal distance 7 mm, skull with parietal bone remodeling, secondary Probable anhydramnios, not ruling out chromosomopathy: anterior corporeal placenta grade II. Being outside the acoustic window by gestational age to assess fetal dynamic structures, concluding however: fetus with evidence of growth pathology, flowmetry evaluated in the territory of the altered middle cerebral artery, high risk of death, with redistribution phenomenon bution (Brain sparing), perceptible high umbilical artery, aortic isthmus without evident alteration. Fetal heart disease, anhydramnios that can increase the risk of maternal mortality, perform resolute conduct according to the ethics committee and consensus with family members are observed.

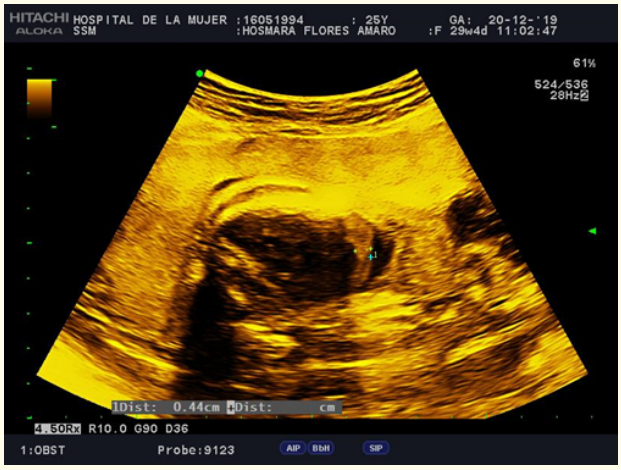

Image 1: *Head screw size vs frequency of usage.*

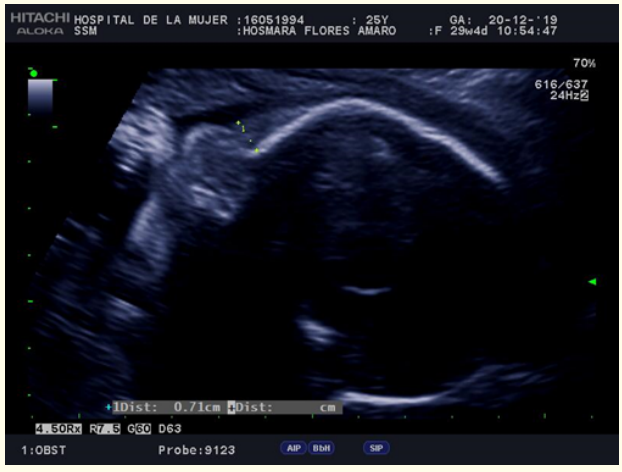

Image 2: *Sagittal section at the level of the fetal profile, nasal bone hypoplasia is observed, with thickening of the skin and a prenasal distance of 7 mm, there is flattening of the frontal bone.*

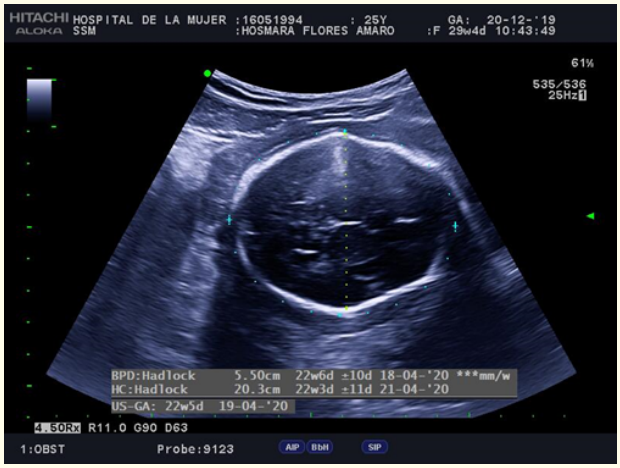

Image 3: *Transthalamic axial cut, showing integrity of the skull with remodeling in both parietal bones, showing an intact midline, as well as the cavum of the septum pellucidum nasal distance of 7 mm, there is flattening of the frontal bone.*

Finally, it was decided to interrupt the pregnancy, due to childbirth, complicated by obstetric hemorrhage, with the following findings: umbilical cord was veiled and friable, at 07:10 on 12.21.2019, a 600gr female live birth was obtained, APGAR 7-8, Ballard 28.2 weeks of gestation, Silverman Andersen 3 due to respiratory grunting, nasal flaring and intercostal retractions, head circumference 22 cm, thoracic perimeter 21 cm, abdominal perimeter 19 cm, brachial perimeter 6 cm, lower segment 19 cm, foot 4.5 cm. FC 130´ FR 60´ temp 36ºC.

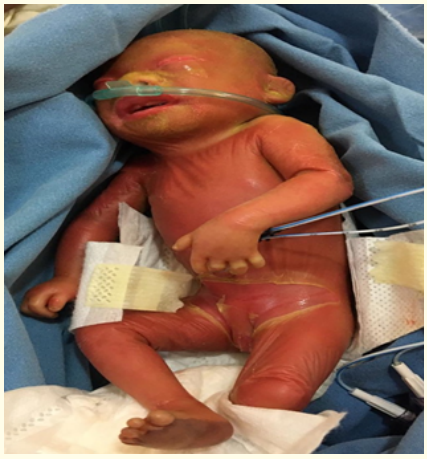

Image 4: *Image of a newborn affected by harlequin ichthyosis, showing the trunk and limbs covered by hyperkeratic plaques with more marked fissuring in folds. In the facial region, the flat nasal root stands out secondary to the hypoplasia of the nasal bone, the palpebral ectropion and the everted lips.*

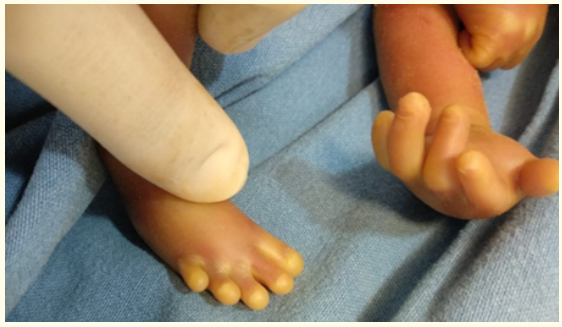

Image 5: *Flexion deformity of both hands and feet.*

Physical examination reactive to manipulation, with data suggestive of Harlequin ichthyosis, with yellow-greyish skin coloration with hyperkeratotic scaling erythematous plaques that simulate patches, deep intertriginous fissures, anasarca, microcephalic skull without alterations on its surface, anterior normotensive fontanel, posterior punctate, hypoplastic ears with low implantation, patent external auditory canal, bilateral ectropion, hypoplastic nasal bridge, patent nostrils, intact lip and palate, normal neck, intact clavicles, chest with data of respiratory distress with Silverman Andersen of 3 at the expense of respiratory grievance, nasal flaring and intercostal retractions, bilateral inspiratory roughness, without aggregates, normokinetic precordium without murmur, abdomen without loop drawing, soft depressible, no megaly are palpable, peristalsis absent, umbilical cord without bleeding, artery-vein ratio 2:1, phenotypic genitalia Entirely female, pudendal and perianal area with no breaks in continuity, patent anus, negative Bar-low, Ortolani and piston hips, intact spine, no midline defects, limbs with good amplitude, hypoplastic hands and feet.

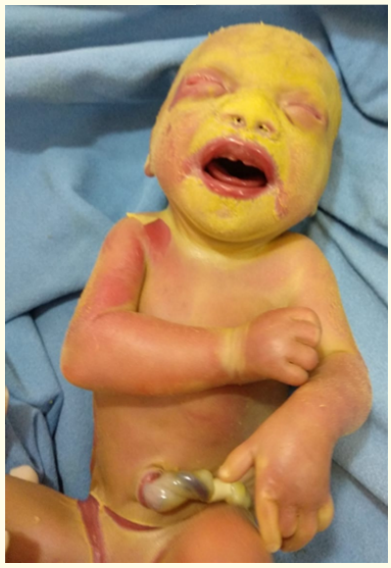

Image 6: *Thick skin with cracks, flexion deformity. Ectropion and eclabium.*

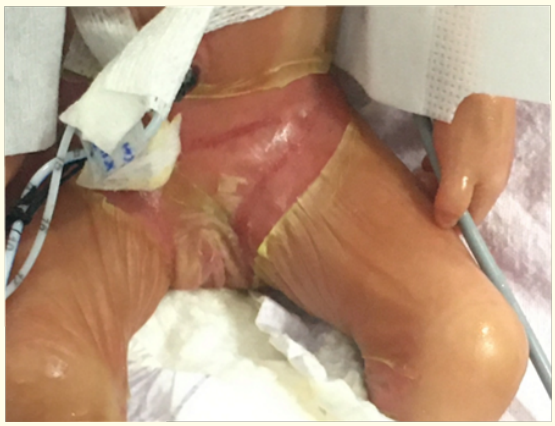

Image 7: *Excessive fluid loss leads to dehydration.*

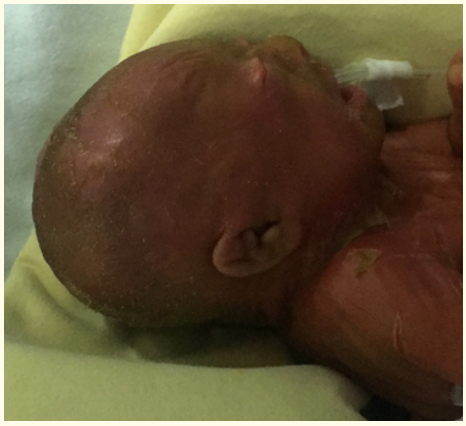

Image 8: *Shock and respiratory deterioration.*

Presenting pulmonary deterioration, requiring surfactant and mechanical ventilation, maximum flows PIP 18, PEEP 5, RF 70, FiO_2 100%.

Abdominal ultrasound (usg) decreased liver size, increased echogenicity, normal suprahepatic veins, portal vein 5 mm, intrahepatic and extrahepatic bile duct without dilations, common bile duct 1.4 mm, gallbladder with anechoic content 1.23 x 0.57 x 0.27 x 2.8 cm, wall 3 mm, spleen morphology normal, kidneys of normal shape, size and location, cortical-medullary relationship preserved, smooth edges without ectasia or stones, right kidney 2.56 x 1.13 cm, left 2.98 x 1.42 cm.

Transfontanelle ultrasound. Without abnormal displacements, normal thalamus and caudate nucleus, cerebellum and parenchyma without alterations, without subdural, subarachnoid or epidural collections, without ventricular dilatation.

In strict isolation in the neonatal intensive care unit, treatment was started with a double antibiotic scheme based on aminoglycoside and beta-lactam, as well as skin care with topical moisturizers, intravenous steroids with mechanical ventilation in conventional modality, fluid support at high requirements secondary to high insensitive losses as well as electrolyte support.

At 48 hours of life, he presented shock data showing pale, hypoactive, hyporeactive, presence of low cardiac output data, starting aminergic support with dopamine and dobutamine, as well as severe metabolic acidosis. He died on 12.23.2019, 9:50 p.m. with diagnoses of congenital ichthyosis, hypovolemic shock, altered hydro-electrolyte balance and extreme prematurity.

Due to sudden deterioration, neither biopsy nor dermatology or genetic evaluation was possible, therefore our case did not have a histopathological or genetic diagnosis, the phenotypic characteristics being sufficient, as well as the high suspicion of chromosomopathy by ultrasound. Advanced performed by maternal-fetal medicine, for diagnosis of congenital ichthyosis.

Conclusion

Therefore, the specialized ultrasound-graphic prenatal assessment with ultrasound is crucial in the diagnosis of congenital ichthyosis, especially in the Harlequin phenotype, since it is the most serious and where alterations can be found, if not confirmatory, if suggestive of the alteration, so its early detection can help detect which patient requires invasive diagnosis to determine DNA mutations either with amniotic fluid collection or chorionic villus biopsy, genetic examination of the parents, as well as genetic counseling.

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