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Harlequin Ichthyosis
(Pathogenesis, Morphology, and Diagnosis)

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Abstract:

Ichthyoses are a group of disorders marked by whitish, brown or dark-brown scales on the skin of almost the whole body. Harlequin ichthyosis (HI) is the most severe form. Neonatal death from HI was once common. Due to intensive neonatal care and, probably, to the early introduction of oral retinoids, Severe ABCA12 deficiency results in malformation of intercellular lipid layers in the cornified layers and leads to epidermal lipid barrier disruption. In HI patients, at least one mutation on each allele must be a truncation or deletion mutation to cause serious loss of ABCA12 function. Identification of the gene underlying HI has enabled DNA-based prenatal diagnosis for HI at the earlier stages of pregnancy with low risk. There are no curative treatments for HI, this report was undertaken with an objectives to review the mutation in (ABAC12) underline the severe congenital skin disease and to know the prenatal diagnosis of harlequin ichthyosis and to describe the pathomechanism of harlequin ichthyosis and the characteristic morphologic abnormality of harlequin ichthyosis detected in amniotic fluid cells.

Introduction:

Ichthyosis are a family of 20 congenital diseases that produce a dense hyperkeratotic Epidermis Harlequin ichthyosis is the most serious and often lethal form of recessive congenital ichthyosis [(1)] Children born with this condition have a hard, yellowish, Thick skin that covers most of their bodies, skin forms large diamond-shaped plates, divided by deep cracks that restrict movement [(2).] And their showing a deep Erythematous cracks, especially on the trunk the constricting skin causes severe ectropion (Lower eyelid eversion) and eclabium (lip eversion).rudimentary ears with retro auricular old loss, and nasal hypoplasia and other clinical features in infant Include palmoplantar keratoderma, alopecia, and persistent ectropion and eclabium. [(3)]

Often common are ophthalmological complications that include chronic conjunctivitis, keratitis of touch, squint, Approximately one-third of patients experience developmental delay in speech and language as well as fine and gross motor skills, and are more susceptible to infection due to the impaired skin barrier function.

The tightened skin may cause difficulty breathing that leads to respiratory failure.

In the past, an HI-affected neonate would often die within days of birth, but patients now have an increased chance of survival with better intensive care and possibly using oral retinoids. [(3).]

HI was registered in a variety of ethnic backgrounds and in both sexes. A variety of other diseases underlie mutations in ABC genes, and also Many disorders include cystic fibrosis, Tangier disease, pseudoxanthoma elasticum, X-linked adrenoleukodystrophy, and Dubin – Johnson syndrome.[(2)]

To treat the condition, removal of scales and regular application of emollient oils. Harlequin ichthyosis is also known by many other names, including fetal ichthyosis, harlequin fetus, harlequin baby, intrauterine ichthyosis, keratosis diffusa fetalis, and this article aim to review the genetic defect (mutation) in (HI) patient.

Aim of the study:

This report aim is to review the mutation in (ABAC12) underline the severe congenital skin disease

Materials and methods:

Ultrasonographic Diagnosis, Fetal blood Analysis, Preimplantation Genetic Diagnosis, fetal DNA analysis[3].

Results:

The combined use of ultrasonography and fetoscopy has been shown to be useful in the prenatal diagnosis of various genetic disorders where the metabolic basis in amniotic fluid cells is either unclear or not expressed. [4].

Analysis of fetal blood for the detection of hemoglobinopathies, chronic granulomatous disease, and classic hemophilia has been reported, and direct fetal visualization for certain malformations [3].

Fetal DNA analysis since the (ABCA12) gene mutation was identified, fetal skin biopsy was replaced by direct DNA sequence analysis using chorionic fetal DNA samples of villus or amniotic fluid [3]. Analysis of DNA has advantages over fetal skin biopsy because it is the most definitive diagnostic tool that can be done earlier and is more widely available It is also possible to compare fetal DNA with parental DNA to delineate pathogenic mutations and to determine uniparental mosaic disomy, nonpaternity and germline after 15 weeks, amniocentesis is done safely, but brings a 1% risk of miscarriage.Chorionic villus sampling can be done at 10 weeks earlier, but is associated with a slightly higher rate of miscarriage [3].

Preimplantation Genetic Diagnosis the discovery of the causative link between ABCA12 mutations and HI has enabled the diagnosis of potential carriers who want to start a family with in vitro fertilization the procedure uses DNA analysis of a 6- to 10-cell embryo blastomer biopsy as well as individual blastomers. A collection of disease-free embryos for implantation is then moved to the uterus this innovative procedure can be used in highrisk families as a preventive measure and avoids termination possibilities.[3]

Discussion:

Genetic defect and the pathomechanism show the mutated protein of interest in HI and a subgroup of ARCIs is the ATP-binding cassette transporter A12 (ABCA12), which carries lipid glucosylceramides through lamellar granules into the extracellular space. Lamellar granules secrete lipid glucosylceramides and hydrolytic enzymes (e.g. proteases, lipases) and proteins (e.g. corneodesmosin) required to desquamate (skin shedding).The lipid glucosylceramides are hydrolyzed to form hydroxyceramides, which are covalently bound to cornified proteins to form the extracellular lamellar membrane needed to maintain the skin barrier. In HI, lamellar granules are skewed, diminished or absent, causing intercellular lipid deposition in the stratum corneum to be disrupted Extreme hyperkeratosis results in the reduced lipid layer as a compensatory mechanism. The skin barrier is compromised, resulting in defective desquamation and permeability that may be responsible for HI complications. Such as sepsis and dehydration. The metabolism of triacylglycerol produces fatty acids for the synthesis of acylceramides and its role has recently been discovered during the formation of a functional skin barrier.[3]

The ABCA12 mutations in HI are combination heterozygous or homozygous and result in the second nucleotide-binding fold between amino acids 2282 and 2467, truncated or missing regions of the C terminal end of the ABCA12 protein.[3]

If the ABCA12 mutation is located in the first nucleotide binding fold between amino acids 1370 and 1554 and results in only one alteration of the amino acid, the less extreme phenotype occurs in the patients.[3]

The defect in this disease leads to changes in morphology, which we can do the prenatal diagnosis and detect the morphological changes, There is no knowledge of the biochemical basis of harlequin ichthyosis. The prevalence of pronounced hyperkeratinisation at birth, however, led us to believe that fetuses were affected by this condition .The 16th to 20th week of gestation will show dermatological anomalies. [4]
In either amniotic fluid cells or fetal skin biopsies, these anomalies could be observed**.** Fetal biparietal diameter scale, and ultrasonographic measurement (3.5 cm). Ultrasonography in real time (ADR, Tempe, Arizona) after diazepam sedation showed
the placenta to extend over the entire anterior uterine wall. A suprapubic insertion site overlying the thinnest portion of the placenta was selected.[4] Under local skinanesthesia .The placenta was shown to stretch over the entire anterior wall of the uterus. A suprapubic insertion site was chosen on top of the thinest section of the placenta. Central anesthesia of the skin for cytological studies and chromosomal analysis, 15 milliliters of amniotic fluid is aspirated through the side arm channel. The trochar and an endoscope were extracted For cytological studies and chromosomal analysis, the sidearm channel aspires15 milliliters of amniotic fluid.[4]
Extracted the trochar and an endoscope was inserted into the cannula's main channel. The fetal thorax was visualized directly through the fetoscope and gently placed the cannula against the skin of the fetus. The fetoscope was withdrawn and a biopsy forceps were added through the cannula (2 mm X 2 mm jaws). A skin biopsy was attempted using ultrasound. nevertheless, only one sample could be collected due to fetal movement. with

no complications, the pregnancy ended. The same process was performed four weeks later. The fetus was clearly visualized on this occasion with its back at the right uterine anterolateral wall. Fetal movement was minimal and successfully obtained three skin biopsies.[4]

Based on the microscopic experiments that were performed 48 h later, the couple were told that harlequin ichthyosis was thought to affect the fetus.[4]

The pregnancy was terminated by prostaglandin F2a intraamniotic injection and the diagnosis was confirmed by histopathological analysis.[4]

During the second fetuscopy, histological analysis of fetal skin biopsies revealed a keratin layer thicker than predicted for this fetus ' gestational age.This premature hyperkeratosis was mostly associated with hair follicles and sweat ducts and developed hyperkeratotic debris plugs. [4]

Granular cells were present focally in hyperkeratosis areas. Skin samples from control fetuses at a comparable gestational age showed an epidermis consisting of squamous epithelium with only a few cells in depth with minimal keratinization.[4] On the right thorax and right flank, biopsy sites have been found. There were easily visible and exceptionally prominent skin marks across the entire surface of the skin; nevertheless, the scaling required in a full-term harlequin ichthyosis was absent. It was unremarkable the mouth, ears, and nails. Skin samples from multiple sites (scalp, back, thorax, thigh and arm) consistently showed similar characteristics of premature hyperkeratosis to those seen in the biopsies obtained fetoscopically.[4]

Conclusion:

Neonate with harlequin ichthyosis developed a mutation in the (ABAC12) which is lead to show the abnormalities in their organs include (eye, lips, ears, extremities, etc.) Using a different prenatal genetic testing we can recognize the harlequin fetus in utero and suspect the way that this serious form of ichthyosis can cause a long-life disease.

References

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