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RESEARCH ARTICLE

A RARE CASE OF HARLEQUIN ICHTHYOSIS; SUCCESSFULLY TREATED WITH ACITRETIN: A CASE REPORT AND LITERATURE REVIEW

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Abstract

Harlequin Ichthyosis is the most serious congenital keratinization disorder. When the children are born, they are enveloped in thick horn armor. They are thick yellow horn plates that tear deeply when they dry out. In the most severe form, the children often die in the first few weeks of life. But there are also many milder courses, whereby there are obviously flowing transitions from collodion baby to harlequin ichthyosis. The skin condition later corresponds to that of a child with severe congenital ichthyosis (ARCI). Similar to the collodion baby, cases of harlequin ichthyosis should initially be cared for in the intensive care unit for newborns and require interdisciplinary therapy. Harlequin ichthyosis is caused by very special mutations in the ABCA12 gene. These mutations also have an impact on survival. If homozygous mutations are present, the prospects are worse than if the parents have heterozygous mutations. Homozygous mutations are often present when the parents are consanguineous.

Introduction:-

Harlequin ichthyosis (HI) is a rare congenital disease, inherited in an autosomal recessive pattern.(1) It can present many challenges throughout a lifetime with a high morbidity and mortality rate.(2) In a view of the high numbers of consanguineous marriages in Saudi Arabia and its great significance in the culture of the country, the frequency of this disease may be higher but probably is under-reported.(3)

Here we present the first case of HI in Makkah, SA in which Acitretin was used as an intervention, achieving good outcomes, improving survival and quality of life. There is strong evidence regarding Acitretin's effectiveness in HI cases. (3), (4), (5)

Case Presentation

A 37 weeks premature baby boy, who was born on 22 September 2019, to a 37 years old Saudi mother and delivered with characteristic manifestations of HI, thick shielded plate-like keratotic scales covering the whole body and separated by deep erythematous fissures. Facial features are distorted by severe ectropion, eclabium, flattened nose, rudimentary crumpled ears, contractures of limbs, and digits. The antenatal period was uneventful, except for the mother who had a history of gestational diabetes. Her blood sugar was controlled with diet only and she was

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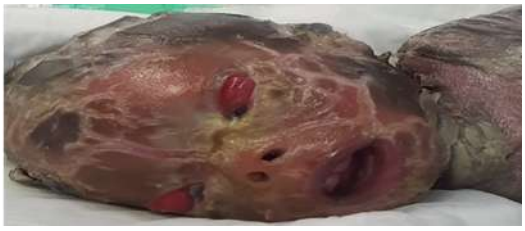
following up in primary health care. The delivery was a scheduled lower (uterine) segment Caesarean section (LSCS), on 22/9/2019 because of breech presentation. Eight years ago, there was a family history of the same condition, his older baby boy sibling, who died in the neonatal period. He has two other healthy sisters and a brother. Mother is a housewife, a non-smoker, lives with her children and husband in Makkah. The parents are consanguineous. The mother does not have any chronic disease, she was not on any regular medication except oral vitamin supplements.

On physical examination, APGAR score was 5,7,8 in 1,5,10 minutes respectively, birth weight was 2.782 kg, length was 53 cm, head circumference 37cm, and abdominal circumstance 32cm. He was vitally stable. Neurological status on the first hour of life: crying and by the second hour and through after, he was either quite alert or quite sleeping, he was active, soft and flat fontanel, normal tone and supine position. Cardiac: normal S1+S2+0. Abdominal: soft, non-tender. Respiratory: equal bilateral air entry. Skin: dense, thick shielded plate-like keratotic scales covering the whole body separated by deep erythematous fissures. Facial features are distorted by severe ectropion, eclabium, flattened nose, and rudimentary ears, with crumpled ear contractures of limbs and digits. (Figure 1a and 1b.

Differential diagnosis: Harlequin Ichthyosis-Collodion baby, a severe form of congenital ichthyosiform erythroderma, Neu-Laxova syndrome, other congenital malformations with microcephaly (lissencephaly and syndactyly).

Investigational results:
O positive blood group. Blood gas: pH:7.30, pCO2:32, HCO3:17.4, BE:10. CBC: Hb:17, Hct:50, WBC:13, Plat:199. CRP:0.258 mg/dl. Electrolytes: Na:143-155, K:3.6-5.6. RFT: BU:1.1-7.4, Creat:30-46, Ca:2.3-2.41. LFT: ALT:133, AST:47, ALT:10.



Lipid profile:
Total cholesterol:1.4, triglyceride:0.94. TORCH: CMV IGM-ve, CMV AB, IGG +ve, Herpes simplex IGG, IGM -ve, Robella IGM N/A. The US of the brain, the abdomen was normal and no abnormalities were detected. Genetic tests and skin biopsy are not done.

Treatment:
on day 1, our patient was incubated on Oxyhood, started on empirical antibiotics due to metabolic acidosis. Feeding was 5 ml Q3hrs with IV fluid and the baby was NPO.

Based on the dermatological counseling, the baby was put on the humidified incubator, ointments BID. The patient started on Acitretin 1mg/kg/day = 2.5 mg syrup PO once daily. Consultations to other specialties (ophthalmology, plastic surgery, pediatric surgery, vascular surgery, and genetic counseling).

Investigations like lipid profile and liver function tests were repeated monthly.

A skin lesion significantly improved, and he was discharged from the hospital at 2 months of age on the 3rd of December to follow up as an outpatient (Figure 2a and 2b). On the 17th of December, the patient was lost to follow up.

Literature Review:-

Harlequin ichthyosis (HI) is the most severe form of autosomal recessive congenital ichthyosis (ARCI).(6) It is characterized by large, thick, plate-shaped scales already present at birth over the entire body, with pronounced eversion of the eyelids and lips and flattened ears and by the later development into severe scaly erythroderma.

The disease is very rare. The incidence is given as less than 1 in 1,000,000 live births. The cause of the disease is an autosomal recessive inherited mutation of the ABC12 gene on chromosome 2 at gene locus 2q35.(7) The gene product is responsible for the transfer of lipids in the skin.

Whitish, plate-like hyperkeratoses that are surrounded by deep furrows or fissures appear over the entire body. Oral and genital mucosa are also affected. Other symptoms are ectropion of the eyelids and lips, as well as restricted mobility of the extremities and thorax with contracture. The affected newborns are sometimes referred to as " snake babies " or " collodion babies " because of their characteristic skin changes. Due to the dysfunctional skin situation, the newborns suffer from a rapid loss of temperature and fluid. You have a significantly increased risk of infection.(8) The defect can lead to life-threatening situations in the first week of life.

Systemic therapy with retinoids (derivatives of vitamin A acid) was started in patients with ichthyoses from around 1977 in Switzerland and Germany.(9) So, there are some patients who have had personal experience with this therapy for more than 40 years.

For treatment with vitamin A acid preparations, it has a number of effects that are mediated directly through the nucleus. A large number of genes are affected by this preparation, but no specific correction of a genetic disorder takes place. In this respect, the therapy with Acitretin or with another retinoid is always a symptomatic or symptom-suppressing treatment, similar to that of course also applies to ointment therapy.(10) The retinoids were originally developed to treat patients with psoriasis or acne. It was only then that it was discovered that patients with ichthyosis also benefit well from it. However, the aim of retinoid therapy should not be to make the ointment treatment superfluous, but to supplement it in a meaningful way.

Before starting therapy, retinoids must be subjected to laboratory and a series of X-ray examinations to rule out a growth disorder. Further x-ray controls may be necessary during therapy, especially if there are symptoms of the skeletal system.(11) The usual dose recommended for Acitretin is generally 1 mg / kg body weight, but the dose must be adjusted individually. In the course of long-term therapy - designed for more than 1 year - one should always aim to carry out an ointment treatment at the same time in order to keep the total dose (cumulative effects) of the retinoids low. It should be noted that even with long-term therapy, laboratory checks should be carried out at least every 3 months.(12) Both the liver and the lipid profiles and the blood count must be checked here. The preparation can cause high cholesterol and triglycerides in some patients.

Treatment with retinoids has a number of subjectively unpleasant side effects, but most of them are tolerable and manageable. These include, among other things, the lip inflammation. Both the nasal mucosa and the eye mucosa

can become noticeably dry.(13) These side effects can be avoided by taking appropriate countermeasures such as the use of lipsticks, nose oil and eye drops are usually well under control and are partly also dose-dependent.

Some patients also develop headaches while taking the drug, which may be an expression of increased intracranial pressure after taking retinoids. In the vast majority of cases, the headache will go away on its own after a while. If it is very severe, however, you may be forced to stop taking the medication. Some antibiotics (e.g., the tetracyclines) can also cause increased intracranial pressure.(14) Therefore, if possible, they should not be combined with a retinoid.

Discussion:-

Harlequin ichthyosis considered the most severe form of congenital ichthyosis with less than 100 cases described in the literature.(4) It is inherited as an autosomal recessive disorder with mutations in the ABCA12 gene has been reported in the majority of Harlequin ichthyosis patients.(15) In the past, harlequin infants rarely survived beyond the first few days of life. However, nowadays with the use of retinoid and advance neonatal care Harlequin fetus can survive (Table 1).

Study Title	Year	Treatment regimen	Outcome
Progress of a harlequin fetus treated with etretinate. (5)	1985	Etretinate was given to a 34 weeks old baby At a dose of 1 mg twice daily, then reduced to 1 mg daily.	At 10 months, there was an improvement of the nose and shape of the ear, there was no eclabium and she moved all joints.
Etretinate in the management of harlequin siblings. (3)	1998	Two male siblings treated with oral Etretinateat at a dose of 1.0 mg three times a day for a one year for the first patient, and until the death of the second patient	In the two siblings who survived for 22 months and 6 weeks. The use of Etretinateat Provides effective improvement regarding the infant skin condition.
The use of retinoids in the pediatric patient. (4)	1998	Oral Acitretin (1 mg/kg body weight/day) was started 10 days after birth and continued for 1 year and thereafter 0.75 mg/kg body weight/day).	Skin showed clinically apparent improvement after about 1 month of therapy. Ability to suckle his mother's breast and the range of movement in all limbs improved. The baby survived to the age of 30 months.
Perinatal management of harlequin ichthyosis: a case report and literature review.(16)	2010	On the first day of life, the patient was given Acitretin, 1 mg/kg /day. Regular follow up investigations were done; including Complete Blood Count, liver function tests, lipid profile, and others.	Several weeks from treatment initiation, the thick hyperkeratotic skin plates started to shed, leaving generalized erythematous ichthyosis. The baby survived; at the time of the report, he was 2 years old.
Treatment of Harlequin Ichthyosis With Acitretin. (1)	2015	Systemic treatment with acitretin was started on the ninth day of life at a dose of 0.5mg/kg/d, increased to 1mg/kg/d after 2 months	The infant presented progressive desquamation, with an improvement of the ectropion, eclabium, and digital contractures, and was discharged from hospital at 8 months.

Table 1:- Summary of previous case reports regarding treatment regimen and outcome.

Conclusion:-

The basic principle of management of HI is good skincare with multidisciplinary approach including pediatric, plastic surgery, Vascular surgery, genetic and ophthalmology, starting of retinoid (Acitretin) as soon as possible with a dose of 0.5-1mg /kg/day, supportive measures and continuous monitoring for adverse effects are essential.

Declaration of Patient Consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's father has given his consent for his child's images and other clinical information to be reported. The patient's father understands that his child's name and initials will not be published, and due efforts will be made to conceal the child's identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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