HARLEQUIN ICTHYOSIS (HI)

Mohammed Mohy El-Din Selim
Hessa Hassan Al-Bou-Ainain
Hamda Al-Ansari
Department of Dermatology & Venereology
Hamad Medical Corporation
Doha - Qatar.

ABSTRACT:

In this text we present two infants born with Harlequin Icthyosis (HI). The first one died few days after delivery. The second one was successfully treated with Tigason (Etretinate) 1mg/kg/day. There was improvement which began after 10 days from start of treatment and the infant was maintained on treatment till age of 3.5 months, when she expired because of chest infection.

Case Reports:

The first report deals with an Egyptian family who had five of their siblings dying because of Harlequin Icthyosis (H.I.). We describe here one male born in 1994 at 35 weeks showing HI. His weight at birth was 2630 grams. His face showed grotesq features with everted eye lids, flat nose and prominent nostrils (Fig.1). The whole body was covered by cracked thick armour like skin and hands and feet look matted (Fig. 2,3,4). He expired few days after delivery. The history showed that the mother was born 1964 and her husband is her first cousin. She gave birth to two HI babies, one female in 1988 at age of 33 weeks and a boy in 1989 at age of 34 weeks and both died after delivery. She delivered two more females with HI at age of 34 weeks one in 1996 and the second in 1997 and both expired few days after delivery. She gave birth to two normal living females - one in 1991 and the second in 1993.

The second report deals with a family who gave birth to two HI infants. One a baby girl born in 2.3.1998 and the second a baby boy born in 3.10.1999 who died 3 minutes after delivery. The mother is from Sudan (F.I.A.M.). She was born on 1974 and has been married to her first degree cousin in 1996. Her husband was born on 1965. We report here her first HI baby girl who was born on 2.3.1998. She had thick fissured thickened skin all over the body and the toes of feet and fingers of the hands were clumped (Fig. 5,6,7,8,9,10,11). She had flat ears and prominent nasal opening and a flat nose, there were no eye lashes or eye brows. The mouth was fish shaped. The infant was treated with Etretinate (Tigason) 1mg 1kg/day. She began to improve 10 days from the start of treatment (Fig. 12,13,14,15). The treatment was maintained and the thick armour like scales were replaced by a fairly smoother skin, the ectropion became less, the mouth had a better appearance and hands and feet improved (Fig.16,17,18). The infant died at age of 3.5 months because of chest infection.

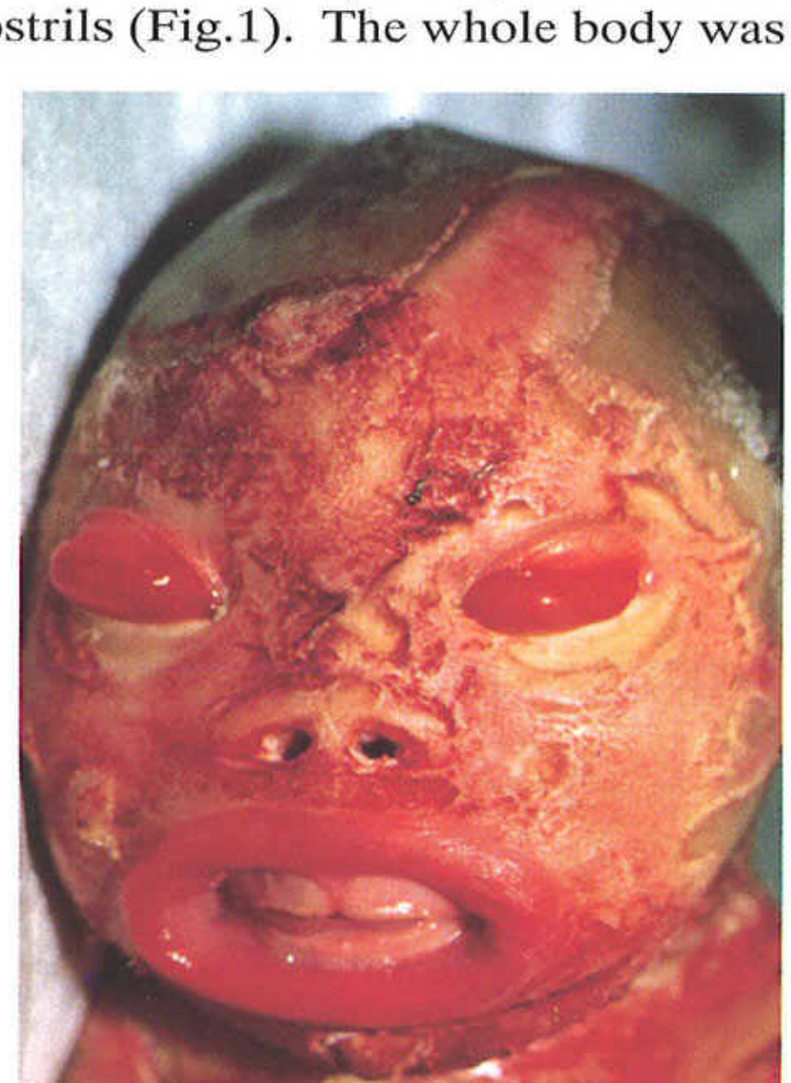


Fig. 1 : HI - first case

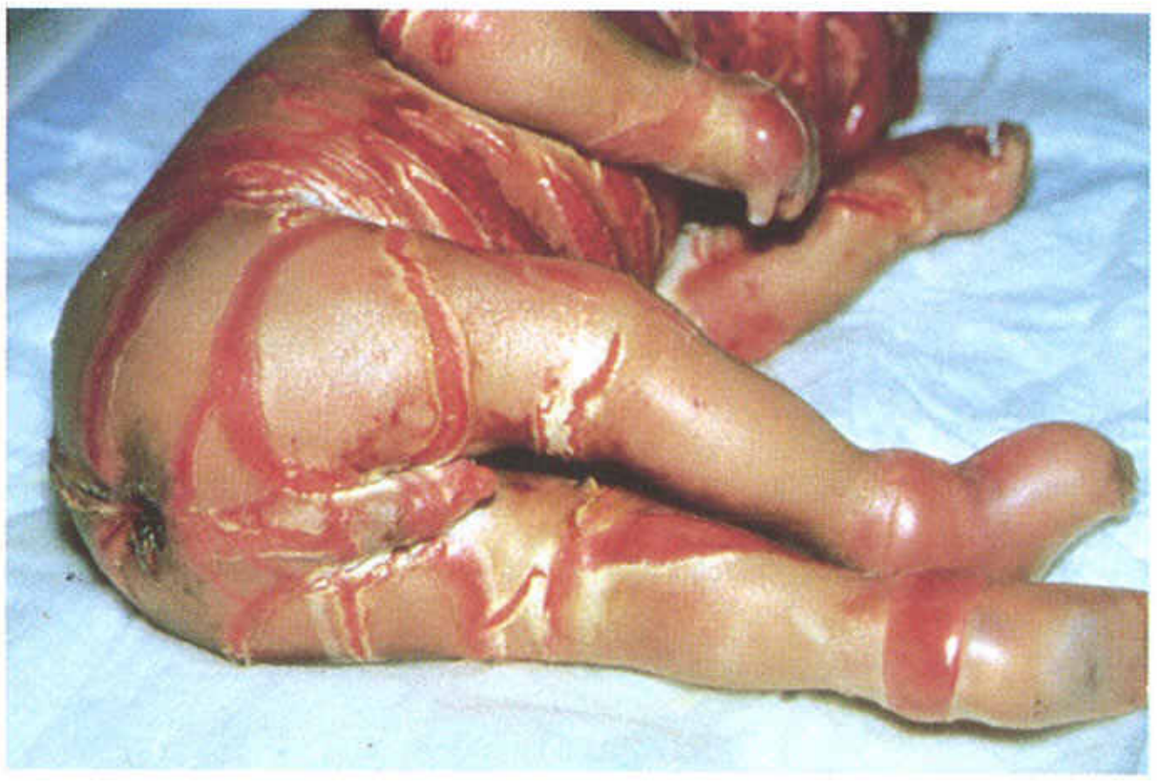


Fig. 2 : HI - first case

Mohammed Mohy El-Din Selim
Consultant Dermatology & Venereology Dept.
Hamad Medical Corporation
P.O. Box: 3050 - Doha - Qatar
Tel. # : 439-3075 / 439-7026 - Fax # : 439-3058

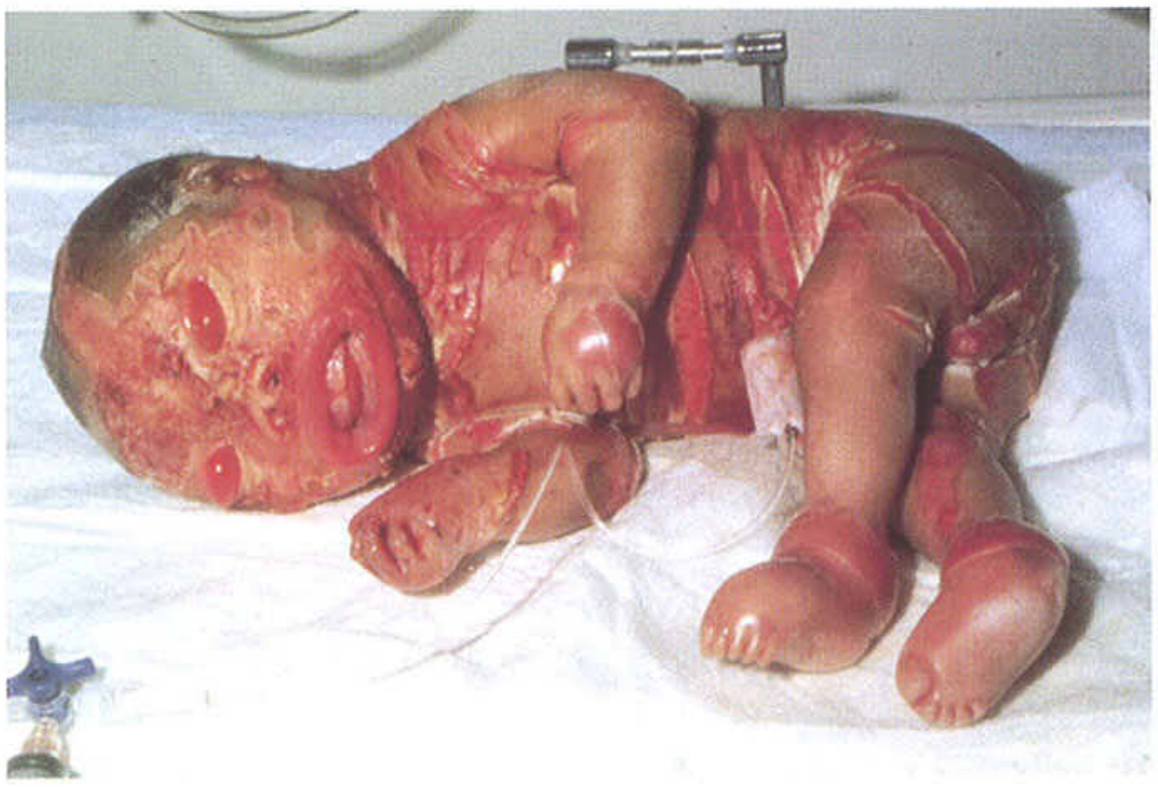


Fig. 3 : HI - first case

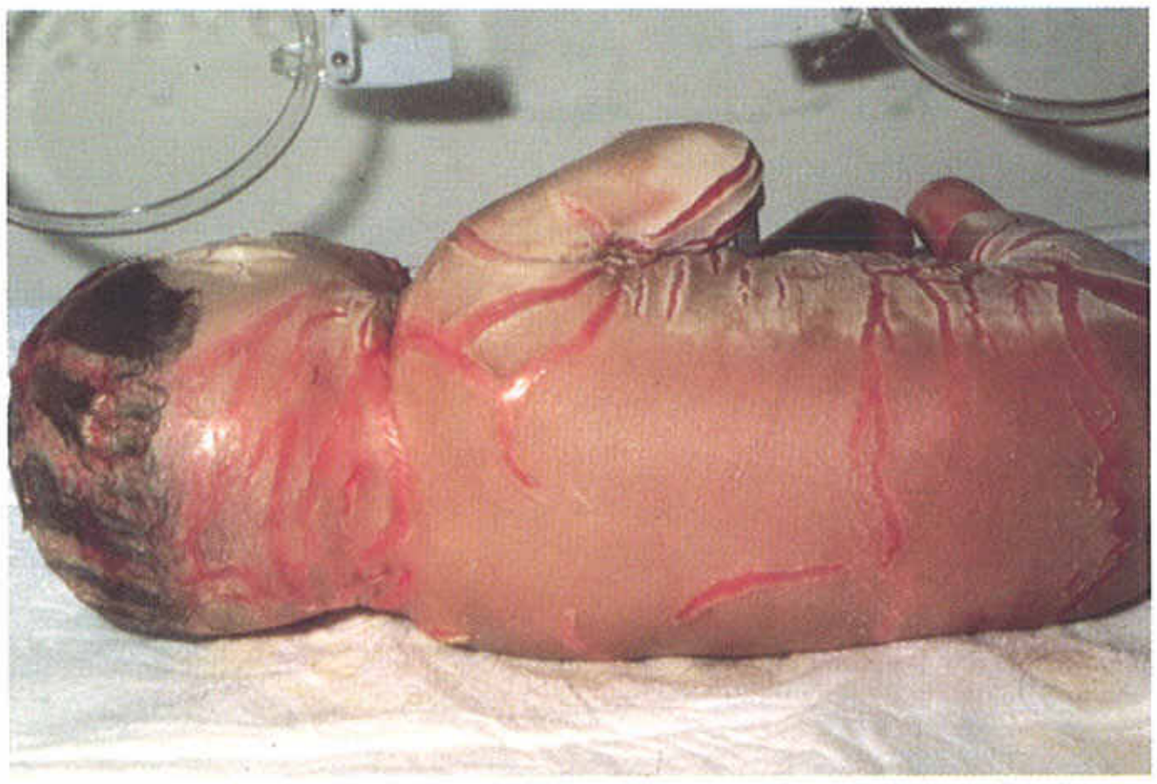


Fig. 4 : HI - first case

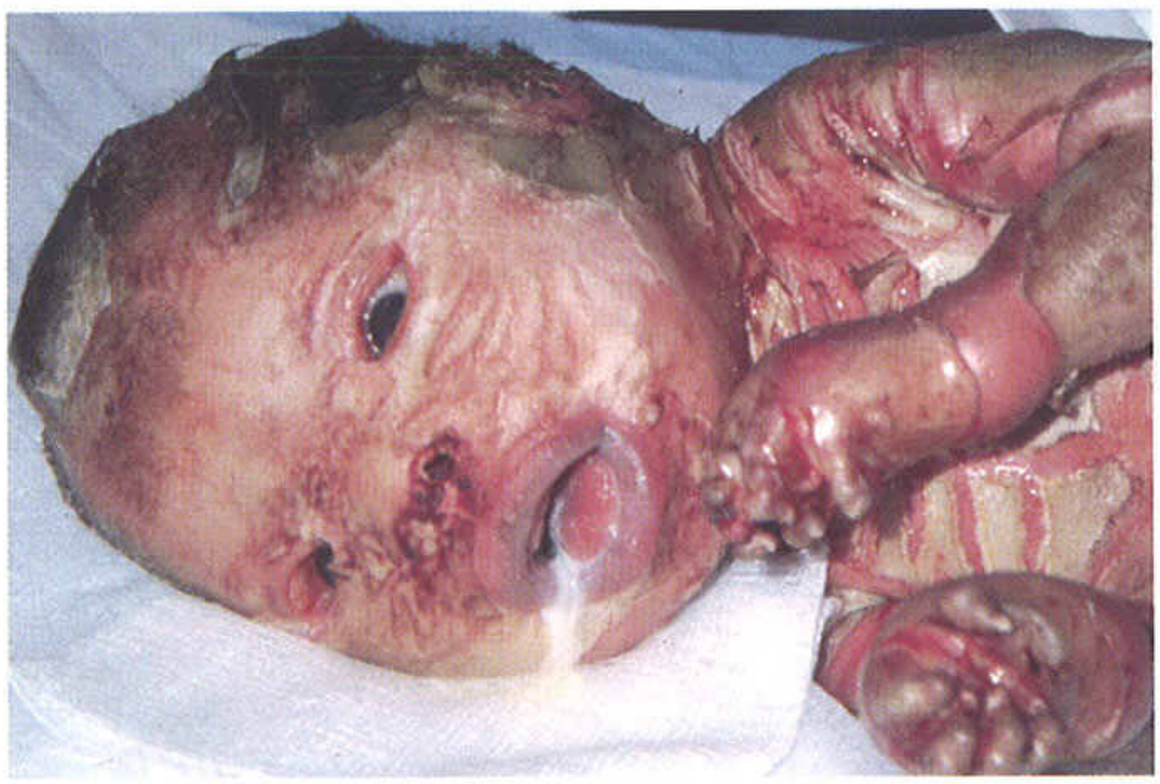


Fig. 5 : HI second case

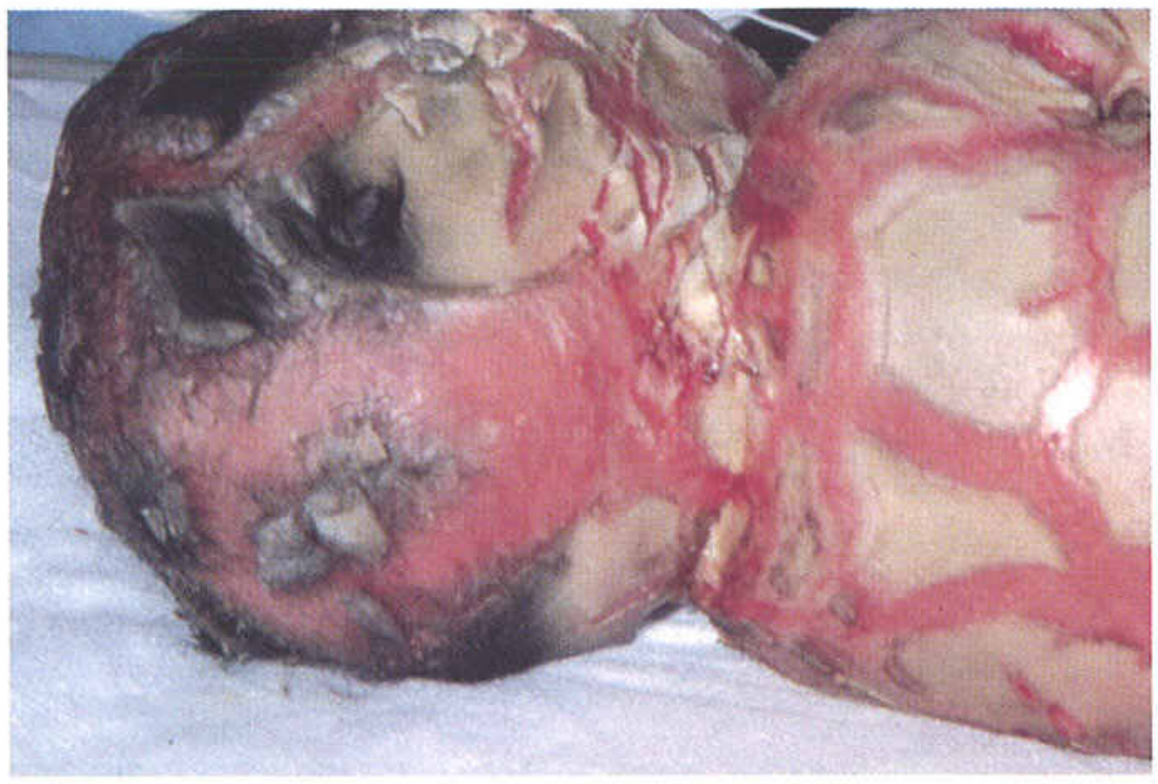


Fig. 6 : HI second case

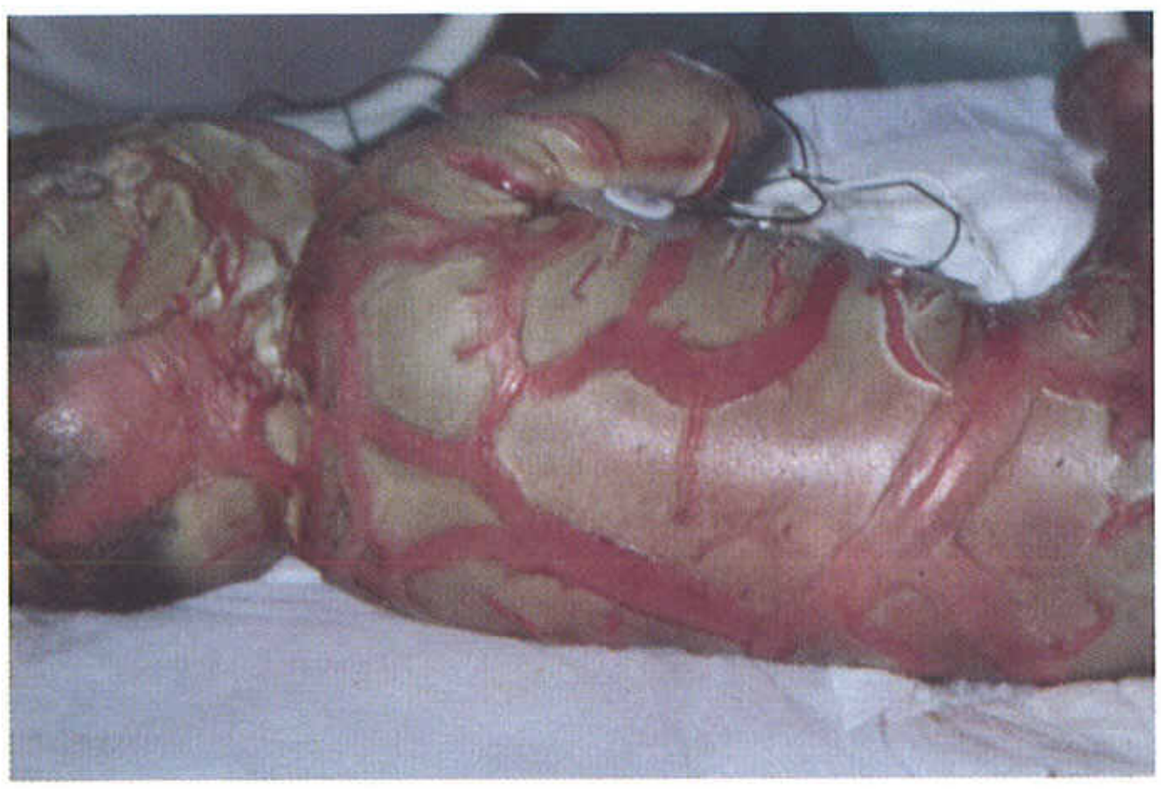


Fig. 7 : HI second case

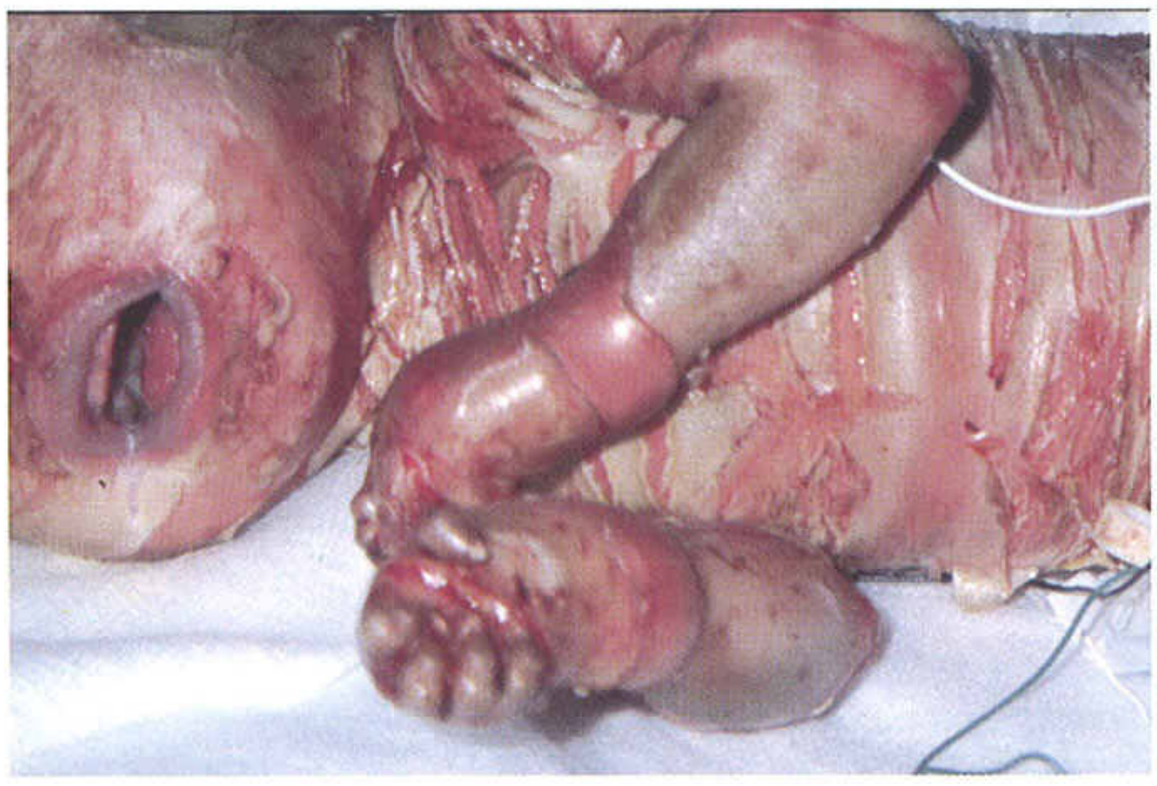


Fig. 8 : HI second case

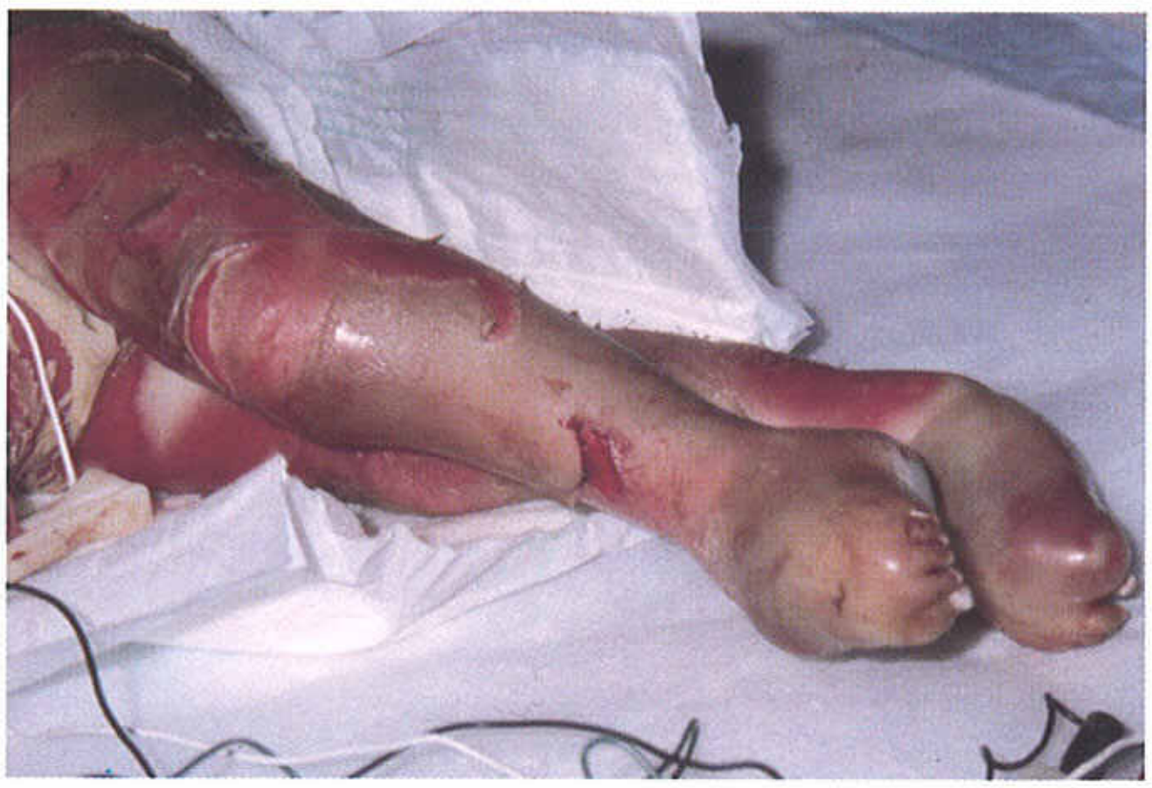


Fig. 9 : Crumbled feet

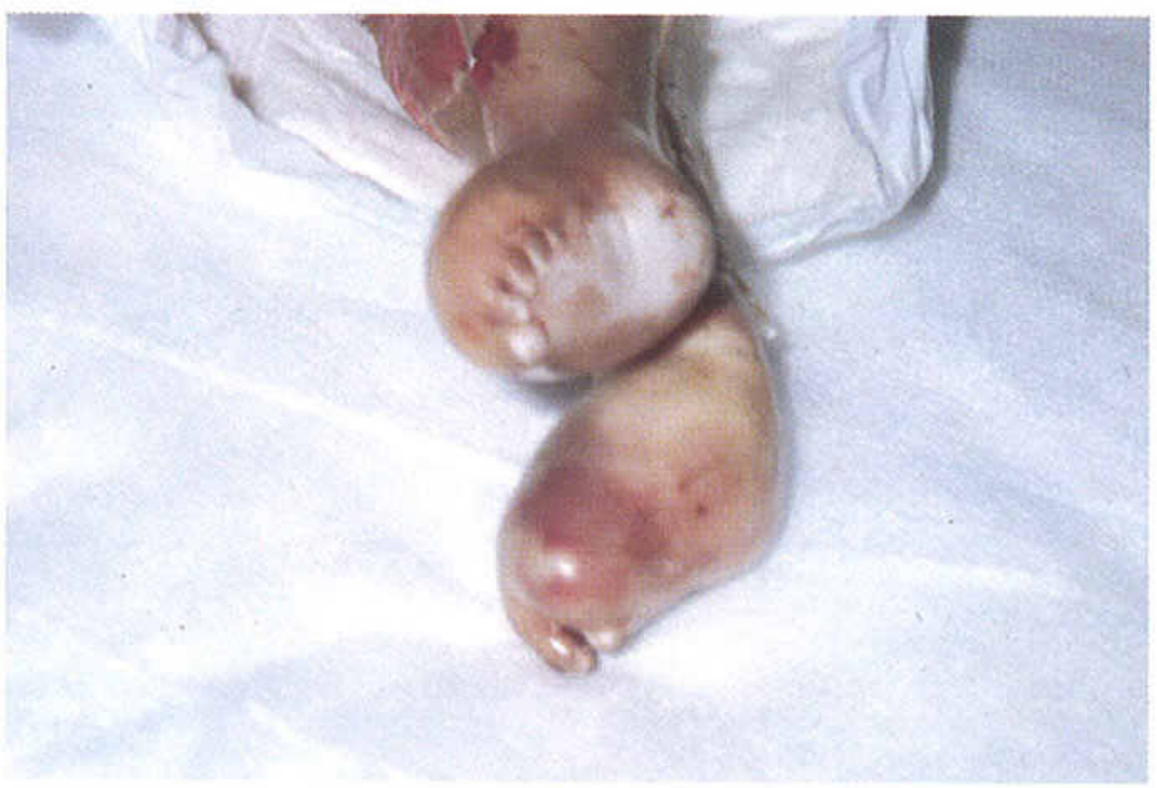


Fig. 10 : Crumbled feet

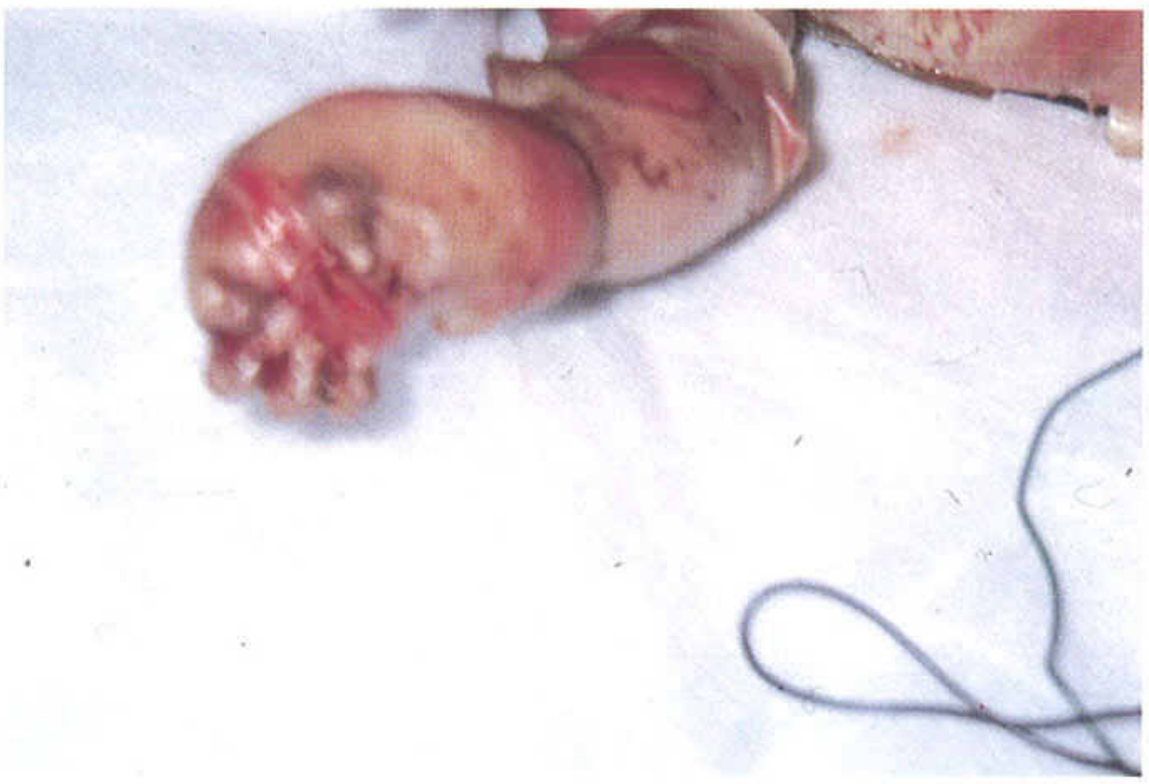


Fig. 11 : Crumbled hand

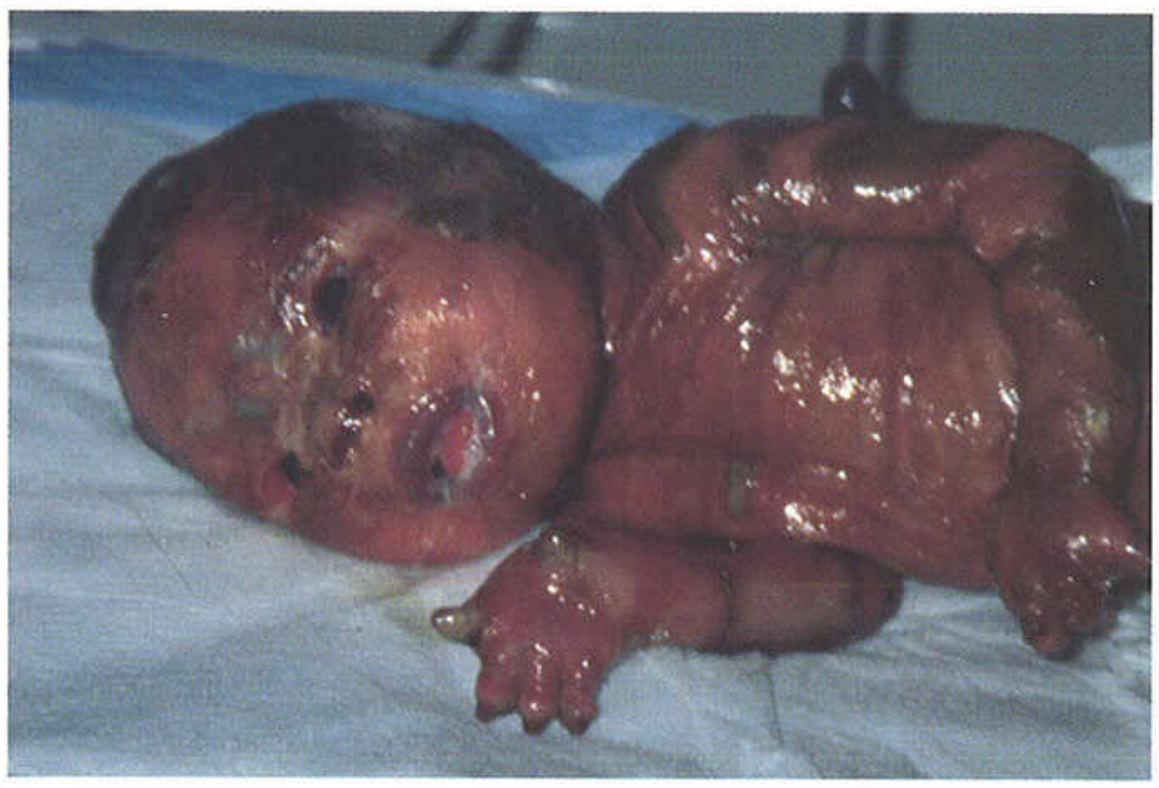


Fig. 12 : Early response after ten days etretinate treatment of the second case of HI.

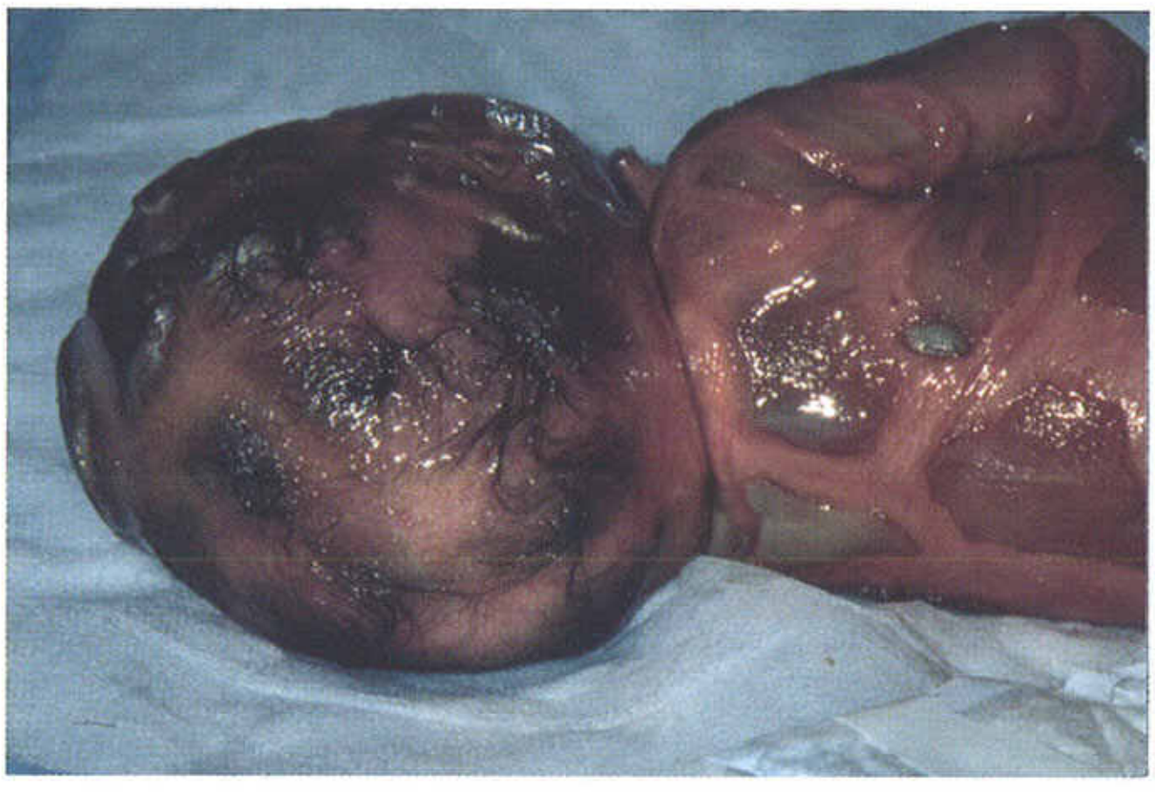


Fig. 13: Early response after ten days etretinate treatment of the second case of HI.

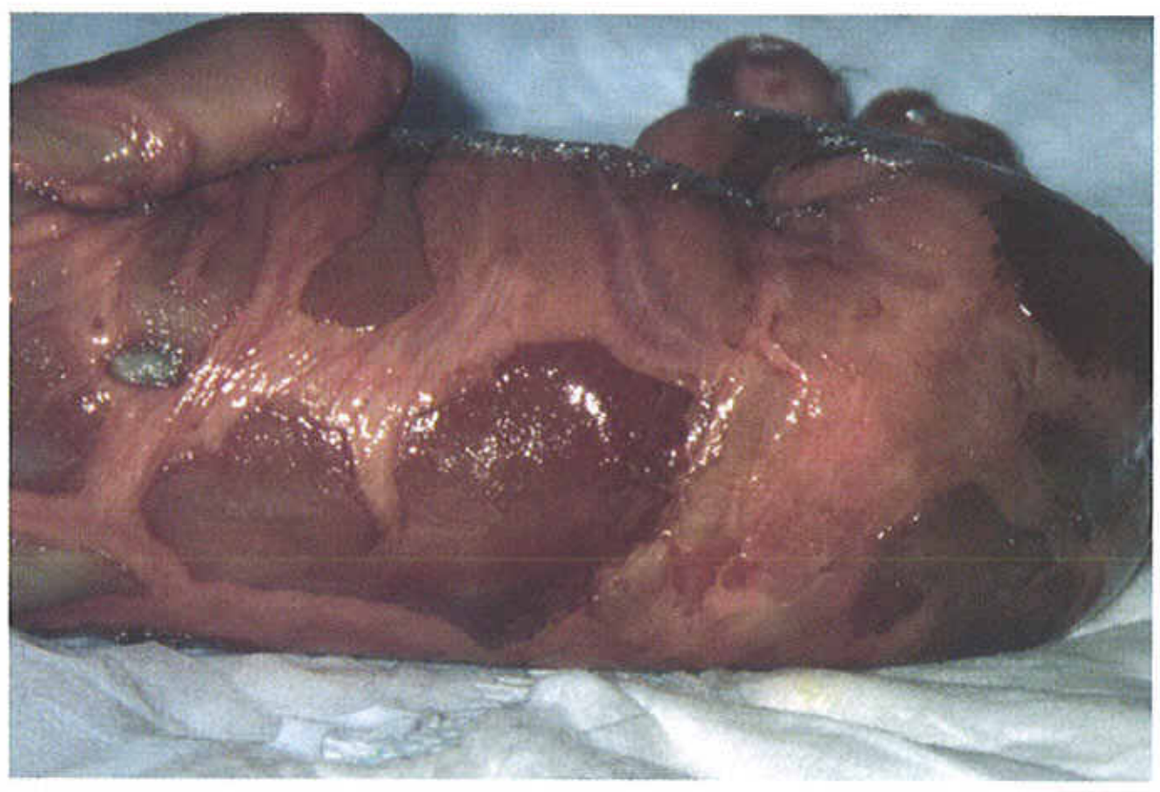


Fig. 14 : Early response after ten days etretinate treatment of the second case of HI.

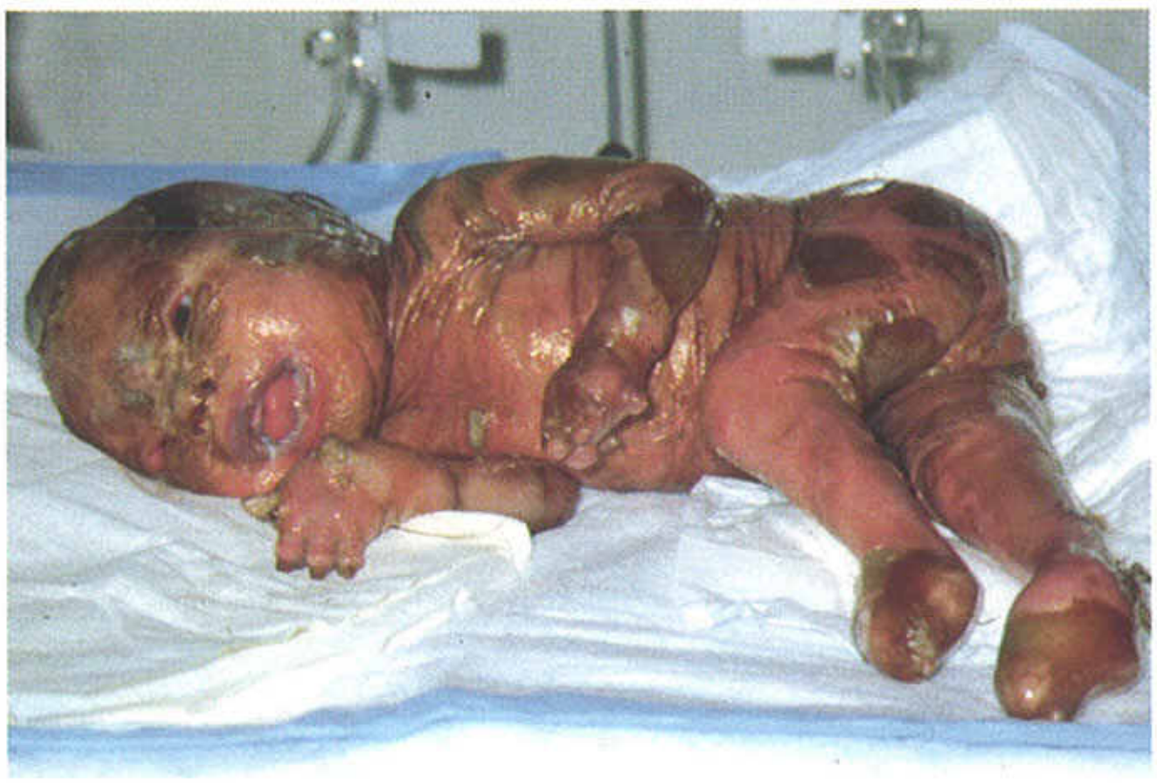


Fig. 15 : Early response after ten days etretinate treatment of the second case of HI.

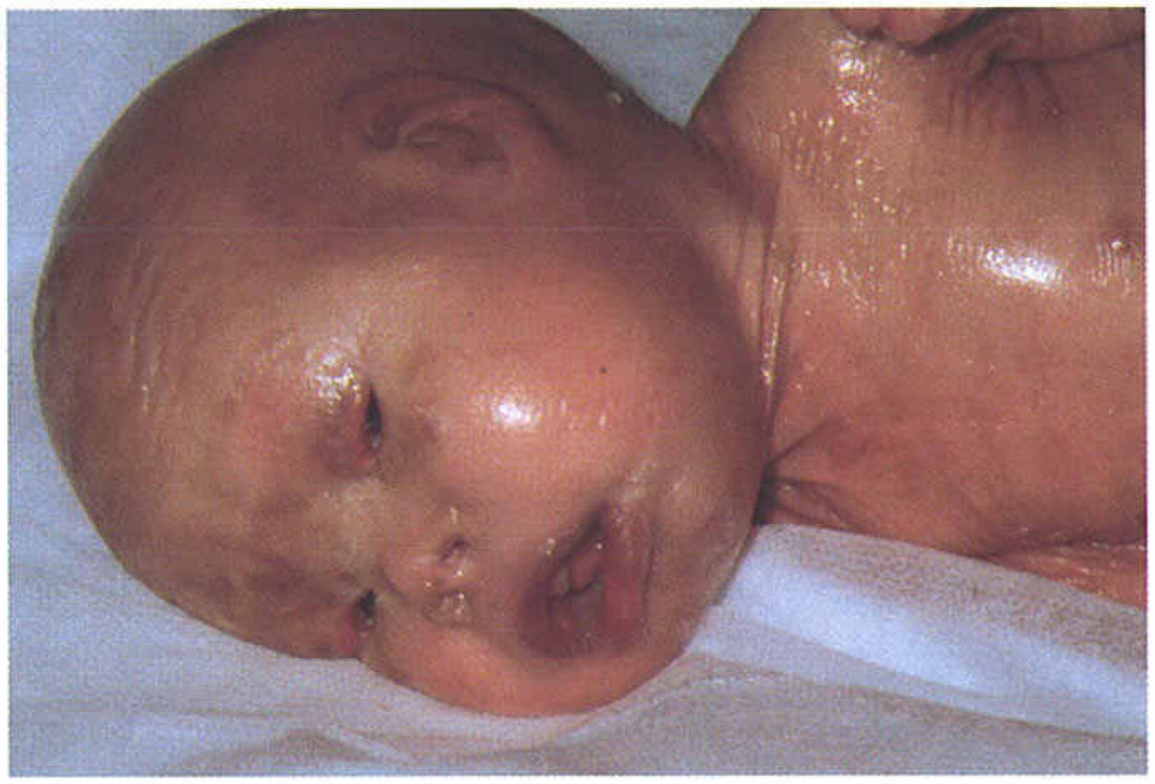
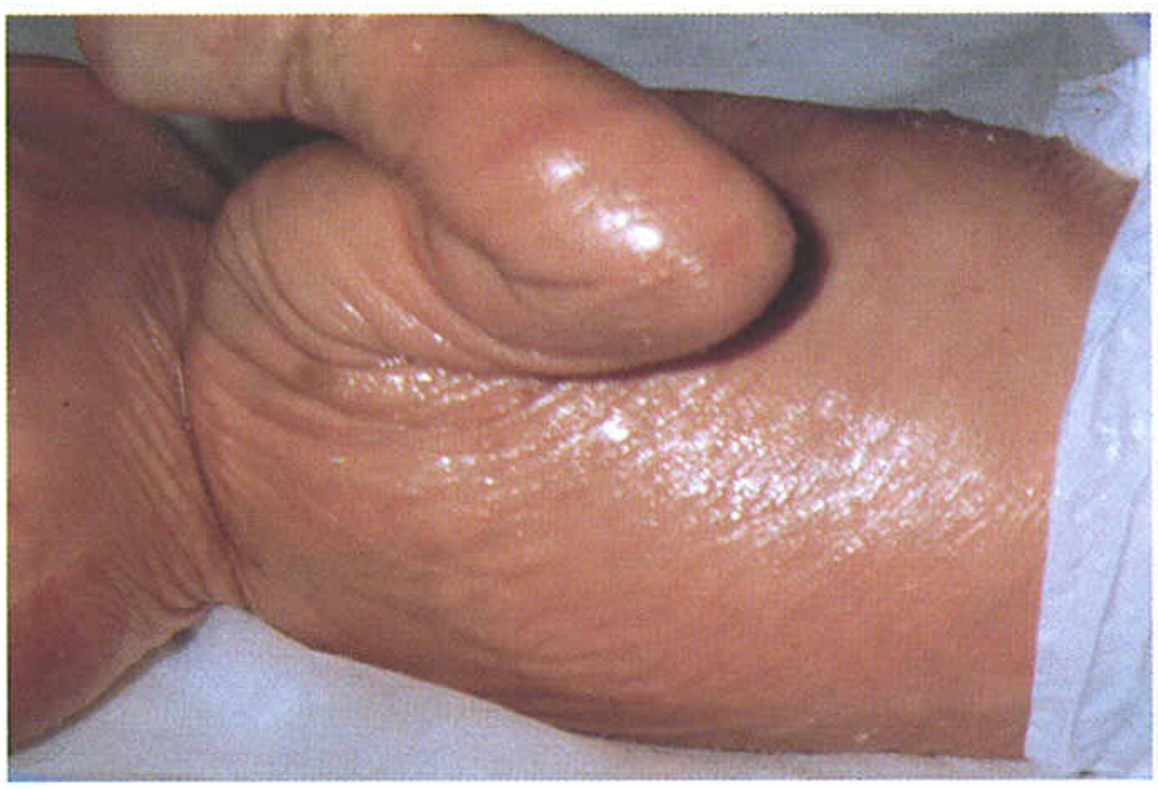


Fig. 16 : a good response with disappearance of HI after 2 months of treatment with etretinate.



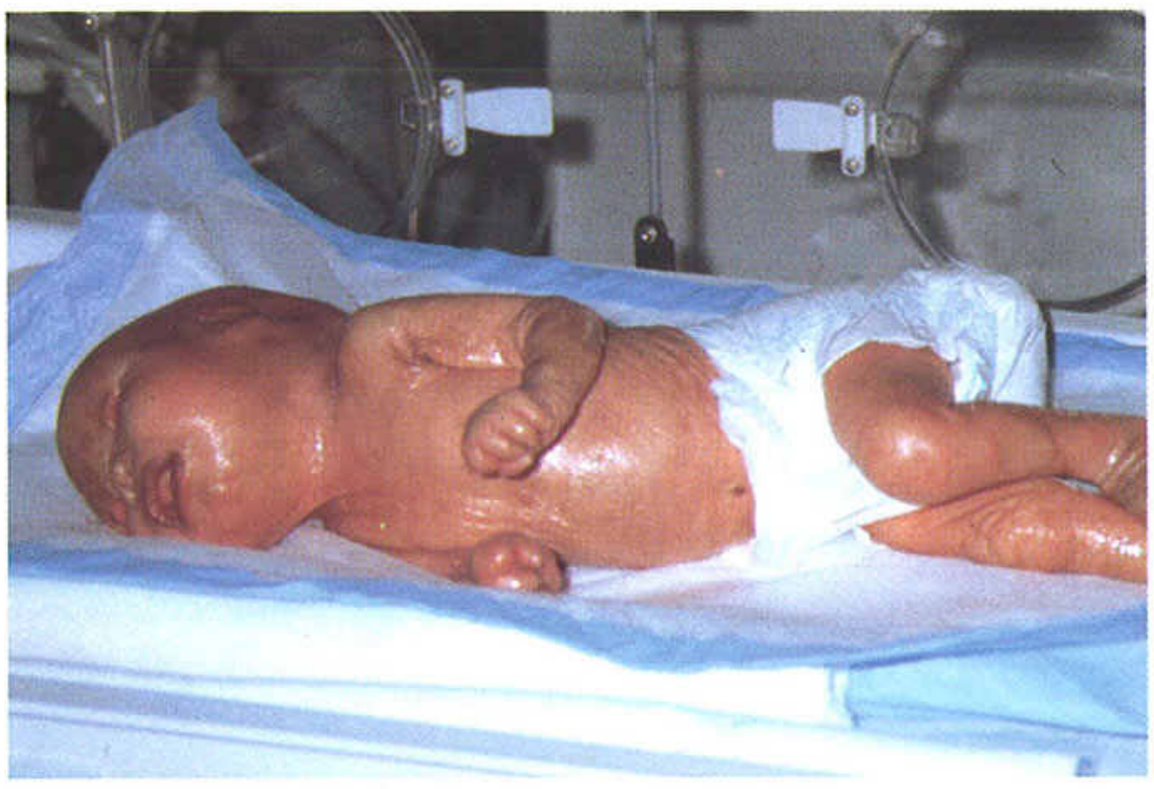


Fig. 17, 18 : a good response with disappearance of HI after 2 months of treatment with etretinate.

Discussion:

Icthyosis is a genetically determined disorder of cornification characterized by generalized scaling. Icthyosis is classified into four major types: two autosomal dominant (ADI) (icthyosis vulgaris and the bullous icthyosis known as epidermolytic hyperkeratosis);the third type is sex linked recessive icthyosis (XI) and the fourth is autosomal recessive icthyosis [1] of which there are 2 main subtypes, the severe form or classic lamellar icthyosis (LI) with thick large dark scales and a milder erythrodermic form known as non bullous congenital icthyosiform erythroderma (NBCIE) with fine white scales [1,2,3].

The collodion baby may be associated with any type of icthyotic phenotype in adults [4,5].

The stratum corneum is formed of bricks of protein enriched and lipid depleted corneocytes surrounded by morter which is represented by an intercellular domain composed of hydrophobic, lipid enriched membrane bilayers and contain desmosomes and a limited array of hydrolytic enzymes.

Defects involving the bricks or the morter may result in abnormal stratum corneum [6].

Alteration in epidermal lipid content or metabolism underlie several scaling diseases [7].

The increased thickness of the stratum corneum in icthyosis is either due to over production by an increased number of proliferative basal cells or due to failure to desquamate with retension of the horny cells [8] as occurs in icthyosis vulgaris and X linked recessive icthyosis [6].

There is evidence that epidermal lipids mediate normal desquamation and have a pathogenetic role in disorders of cornification[7,9,10,11]. The stratum corneum barrier function regulates epidermal cell proliferation, for example acquired icthyosis has been observed as a side effect in patients treated with hypocholesterolemic agents[12], The skin in essential fatty acid deficiency shows acquired icthyosis and exhibits deficient barrier function which is responsible at least in part for the epidermal hyper proliferation[6].

The barrier function is maintained in the epidermis by linoleic acid [13].

Cholesterol sulfate comprises 5% of the total lipid of stratum granulosum in normal skin and is less so in nucleated epidermal layers and stratum corneum[14].

Cholesterol sulfate is lower in the outer stratum corneum than it is in the whole horny layer because normal desquamation is accompanied by continuous hydrolysis of cholesterol sulfate by the enzyme steroid sulfatase in the membrane regions of stratum corneum sheats [15].

In X linked recessive icthyosis (XI) the steroid sulfatase enzyme activity is absent in all nucleated epidermal layers and in the stratum corneum[14] resulting in accumulation of cholesterol sulfate in the skin. It is estimated that the scales in (XI) contain five fold increase in cholesterol sulfate and a 50% decrease in free sterol content[16] and scaling is attributed to delayed desquamation.

Harlequin icthyosis (HI) is autosomal recessive[17] with a chance of 1:4 of each subsequent child to become affected. (HI) like collodion baby may have different causes [18] and may be the phenotypic expression of several genotypes. It is possible that HI is a severe manifestation of NBCIE[19,20,21]. Some believe that in HI mutation exists at a different locus to that involved in NBCIE because if HI were phenotypically a severe form of NBCIE one would expect HI and NBCIE to occur in the same family which so far is not reported [22]. New dominant mode of inheritance was also suggested [23] in HI.

HI fetuses are affected in utero and prenatal ultrasonographic diagnosis was possible by observing a large oval wide open mouth, hypoplastic nose with two holes representing nostrils, eyes appear as two budding lumps, lack of fetal breathing movements, edematous like limb and clumps of keratinized cells in the amniotic fluid [24,25,26]. Prenatal diagnosis (PND) of HI is helped by fetal biopsy [27,28,29] at 21-22 weeks of estimated gestational age (EGA). Hair canal keratinization is thought to occur around 15 weeks of EGA before keratinization occurs in the interfollicular skin. The characteristic abnormalities of HI are known to be more expressed in the hair canal. Electron microscopic (EM) examination of fetal skin biopsy from a fetus at risk of HI demonstrated abnormal vacuoles in keratinized cells and malformation of lamellar granules in the hair canal and clumps of aberrant keratinized cells containing lipid droplets were seen in the amniotic fluid[30].

Immunoblast study of the epidermal extracts revealed the profilaggrin to be more prominent than filaggrin in all the hairy skin regions where hair canals were extensively keratinized [31] and these findings made PND of HI possible at 19 weeks of EGA[30]. A fetus at 16 weeks of EGA had no signs of keratinization and the corneocytes showed only large mitochondria [32]. The amniotic fluid contains clumps of keratinized cells from HI and show disease specific changes. So morphologic analysis of amniotic fluid cells can provide information for PND of HI [33] even as early as 17 weeks of EGA where the source of keratinized cells comes from the intraepidermal part of the hair canal [34].

Development of noninvasive PND appears to be possible by using an in vitro fertilization technique and taking a biopsy from the 6-10 cell embryo (Blastomere) and doing DNA analysis. Using a single fetal cell from the maternal blood such as nucleated red cell has become a technically possible method for non invasive diagnosis of PND [35].

Harlequin icthyosis is rare with less than 100 cases described in world literature [36]. It is usually lethal within the first few days or weeks of life [23,37]. They die within few weeks due to sepsis and respiratory difficulty [38], but long survival to 2.5 years[39] and 9 years were reported [39,21]. Many races and ethnic groups were affected with no sex preference [23]. Four siblings in one family were reported to have HI three males and one female [40] and HI was reported in twins [41]. We report in this text one HI boy a product of a family who has five of their seven siblings showed HI two males and three females. The second case included in this report is a sister of another HI boy and both died.

HI is characterized at birth by massive armour plate like scales over the body surface. The scales

are separated by fissures. The scales distort the facial features resulting in severe ectropion of eyes, eclabium and distortion of the nose and absence or rudimentary ears [18]. Fish like appearance of the mouth, ears without auditory canals which were covered by hyperkeratotic plug [42], hands and feet appear swollen and crumpled.

HI was reported associated with polydactyly and renal abnormalities [43], shortening of long bones [micromelia][44], patent ductus arteriosus and enlarged thymus [45,46]. Examination of blood smears from all cases of icthyosis is advisable in order to screen for leukocyte vacuoles seen in Chanarin-Dorfman syndrome which is a neutral lipid storage disease characterized by congenital icthyosiform erythroderma and leukocyte vacuoles[46]. H.I. is inherited as autosomal recessive form of icthyosis. Classification of the autosomal recessive icthyosis has been particularly difficult because of the large variety of clinical expression and the lack of specific morphological and biochemical markers [47]. Elevated scale n-alkanes in Conjugation with decreased free fatty acid/triglyceride content characterizes autosomal recessive nonbullous congenital icthyosiform erythroderma[48].

The main clinical feature in HI is extensive hyperkeratinization due to proliferation and retention of horny cells. This lack of desquamation could be due to a defect in lamellar body secretion [6,49,31]. Lamellar granule lipids contribute to intercellular lamellae and their enzymes are thought to assist in modification of these lipids within the extracellular spaces aiding in establishing of permeability barrier and desquamation of cornified cells [6,50]. Lamellar granules are lipid rich organelles present in epidermal granular layer and are absent or abnormal in HI and no intercellular lamellae could be detected thus resulting in stratum corneum retention in HI [48]. The keratinocytes contained giant mitochondria which may be related to abnormal lipid metabolism of keratinocytes which consequently may affect composition of lamellar granules in Hi [51].

Both epithelial and mesenchymal elements of skin from HI are affected with primary abnormality in the keratinocyte [52]. The keratinocytes in HI have reduced activity of the serine / threonine protein phosphatase [53,54].

HI is due to an inborn error of epidermal keratinization and responsible genes have not yet been identified [30] and the underlying molecular basis is not understood [23] and may be related to mutations affecting pattern of phosphorylation [23].

Keratins and cornified cell envelope proteins are normally expressed in HI while malformation of the cornified cell envelope as a result of mutation of keratinocyte transglutaminase has been found in lamellar icthyosis [LI][55].

Transaminase-1 gene mutations were identified as causative genetic defect in (LI). HI may spontaneously develop into nonbullous congenital icthyosiform erythroderma (NBCIE) [56] or as a result of retinoid treatment [57]. However abnormal lamellar body production and abnormal lamellar granules in the granular layer and defective or abnormal filaggrin processing are not of the criteria diagnostic of NBCIE [56,57,58].

Study of the epidermal protein shows that K5 and K14 are present in the cells of stratum basale; K1 and K10 in the spinous cells, K6 and K16 are increased in hyper proliferation conditions [23]. Profilaggrin which is a highly phosphoretated protein is a major constituent of keratohyalin in the granular cell layer. During transition from granular layer to horny layer profilaggrin is dephosphorelated and cleaved by proteases usually protein phosphatase 2A (PP2A). PP2A is present throughout the epidermis and is especially strong in the granular cell layer.

PP2A acts on profilaggrin and cleaves it to filaggrin in keratinocytes and this leads to aggregation of keratin and normal cornification. In (HI) filaggrin is absent. The PP2A dependant conversion of phosphorylated profilaggrin to non phospharylated filaggrin is blocked in (HI). Keratinocytes from HI showed lower protein phosphatase activity in culture [54].

PP2A regulates cholesterol synthesis by activating the enzyme 3 hydroxy 3 methyl glutaryl coenzyme A reductase (HMGCoA).

Cholesterol + Fatty acids acted upon by HMGCOA which is activated by PP2A ——> Lamellar granules ——> intercellular lipid lamellae ——> desquamation.

PP2A could be a link between lamellar granule synthesis and profilaggrin processing. (profilaggrin + PP2A —> filaggrin —> aggregation of keratin —> normal cornification.

The gene that controls PP2A is located on chromosome 11. Analysis of genetic DNA from affected

families is currently done to get more evidence of its role in HI [23].

Knowledge of the genetic defect will result in the ability to diagnose the nature of the inherited disorder and to improve prenatal diagnosis, expand the knowledge of the defect and the potential of its treatment.

HI was found to evolve to erythrodermic icthyosis clinically similar to non bullous congenital icthyosiform erythroderma NBCIE) but with persistance of abnormal lamellar bodies production and defective filaggrin processing characteristic of HI but not described in NBCIE [57].

Aromatic retinoids have been used successfully in treating HI starting in the immediate neonatal period [21,57,59]. It gave good results with disappearance of ectropion, eclabium and reduction of the hyperkeratosis [59,60,43,61,62,63,64,65].

Summary :

Two HI infants were presented. The first was a boy born to a family with consanguineous marriage with seven siblings five of whom had HI (3 females and 2 males). The second case was a female born to first cousin parents who had two HI infants (a sister and her brother). The girl was teated with Etretinate (Tigason-Hoffmann La Roche) in the dose of 1mg/kg body weight/day with fairly good effect on the icthyosis but she expired at age of 3.5 months because of chest infection. In this report the history revealed an autosomal recessive inheritance in all HI affected infants and the disease had a fatal outcome in all cases. Etretinate (Tigason) is a promising drug and is known to revert the severe fatal HI into milder erythrodermic icthyosis and better life expectancy.

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Announcement :

Name of the Conference	:	**11th South Zone Conference of Indian Association of Dermatologists Venereologists & Leprologists**
Date	:	**5, 6 & 7th October 2001**
Venue	:	**PSG Hospitals, Coimbatore**
Organizing Secretary	:	**Reena Rai**
Chairman Scientific	:	**C R Srinivas**
Address for Correspondence	:	**Department of Dermatology, PSG Hospitals, Peelamedu, Coimbatore, Tamil Nadu, India. Phone : 570170, Ext.472 Fax : 91-422-594400 E-mail: psgimsr@md3.vsnl.net.in**