Ichthyoses

Dr Rajendra Shinde
Professor and Head
Dept of Dermatology
Mimer Medical College
Talegaon Dabhade

Introduction

- Fish like scaling (heterogeneous group)
- Ichthyoses –scaling , erythroderma- erythema & hyperkeratosis but less scales
- Infections and water loss major concerns
- Syndromic and non syndromic
- ARCI (AR Cong. I) [eg LI]
- Keratinopathic (keratin mutation) [eg EI]
- Most at birth or infancy
- Cl Fs+inheritance pattern+biochemical & molecular abnormalities--------> diagnosis
- Therapy symptomatic with emollients, retinoids

Ichthyoses vulgaris (Auto-semidominant)

- **FLG gene (Filaggrin)**
- Heterozygous (mild) & homozygous (severe)
- Normally profilaggrin(KH granules) →filaggrin peptides →water retaining AA like histidine (natural moisturiser)
- filaggrin peptides aggregates keratin intermediate filaments (cpmplexes) →cross linking to cornified cell envelops →proper compact squamous cells
- Filaggrin deficiency leads to impaired cornification, ↑transepidermal water loss, ↑allergen & irritant penetration → inflammation
- FLG mutations also ass. with atopic , hand eczema, nickel CD, ICD
- ↓urocanic acid (histidine metabolite-photoprotective) →Vit D levels↑↑↑

Ichthyoses vulgaris

Mild : -child fine white extremities scales
-adherent centre & detached edges
-flexural sparing
-PP hyperlinearity (mild hyperkeratosis)

Severe : Birth –mild erythema & generalised scaling
large lamellar like scales later (Neck spared)
extremities, trunk ,forehead, cheeks++
PP fissures & pain (Severe hyperkeratosis)

Summer (high humidity)→improve

Winter (low humidity) →worsen

Associated with KP & atopic (25-50%)

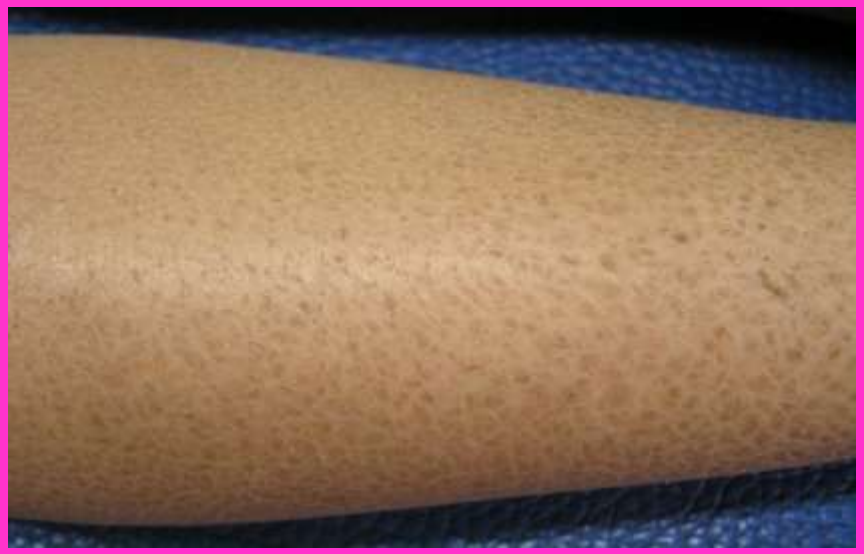
Hpe : ortho. Hyperkeratosis, ↓granular layer

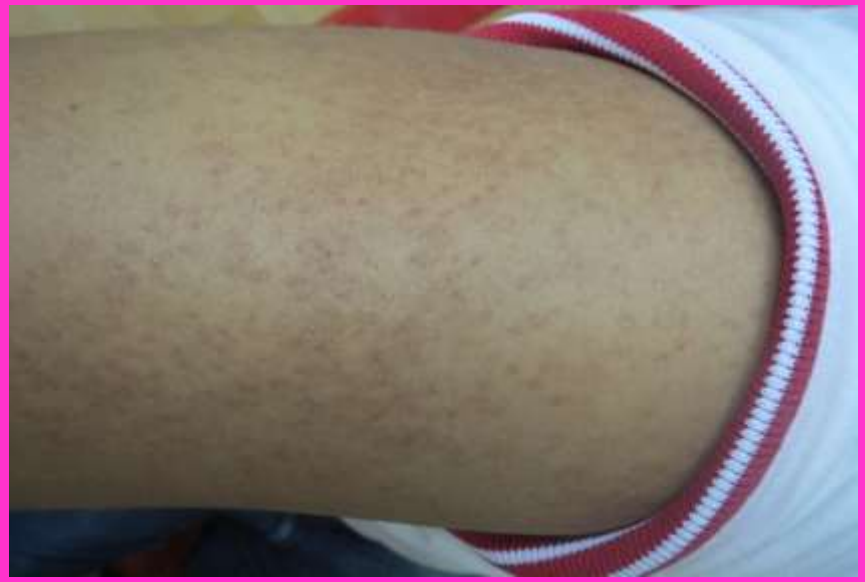
Immunohistochem : filaggrin absent

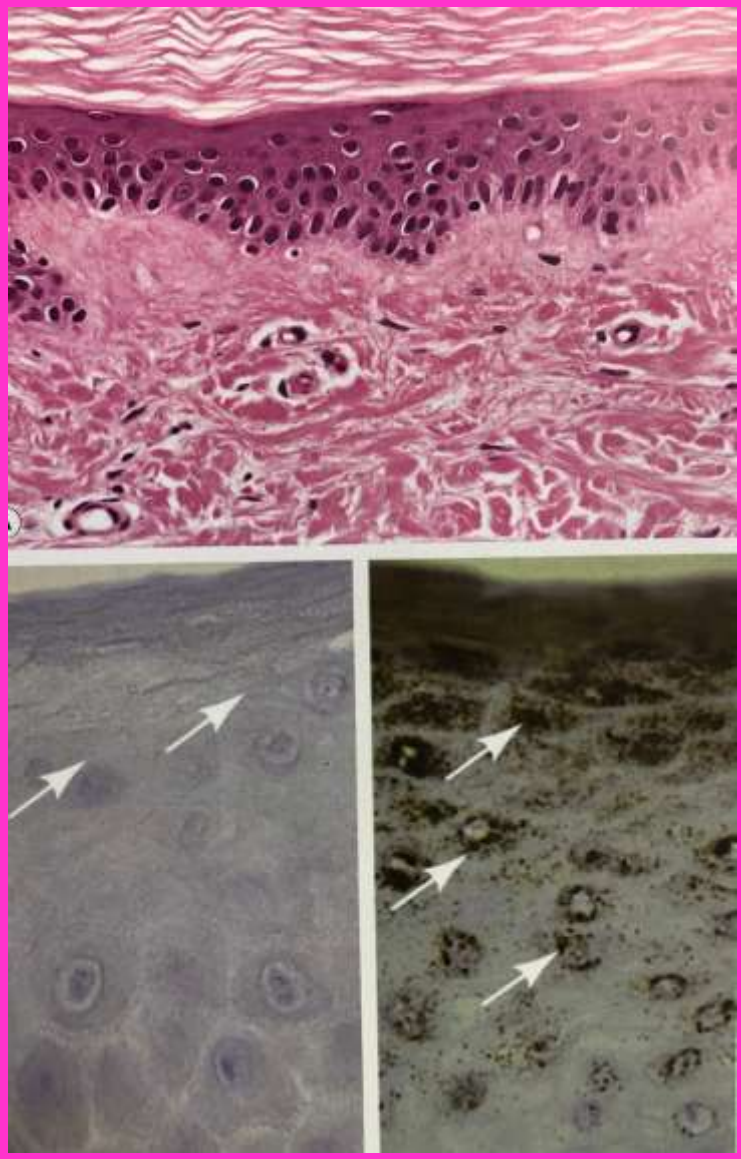
DD: X-linked & acquired (but later in life)

Treatment : emmolients, humectants & keratolytics

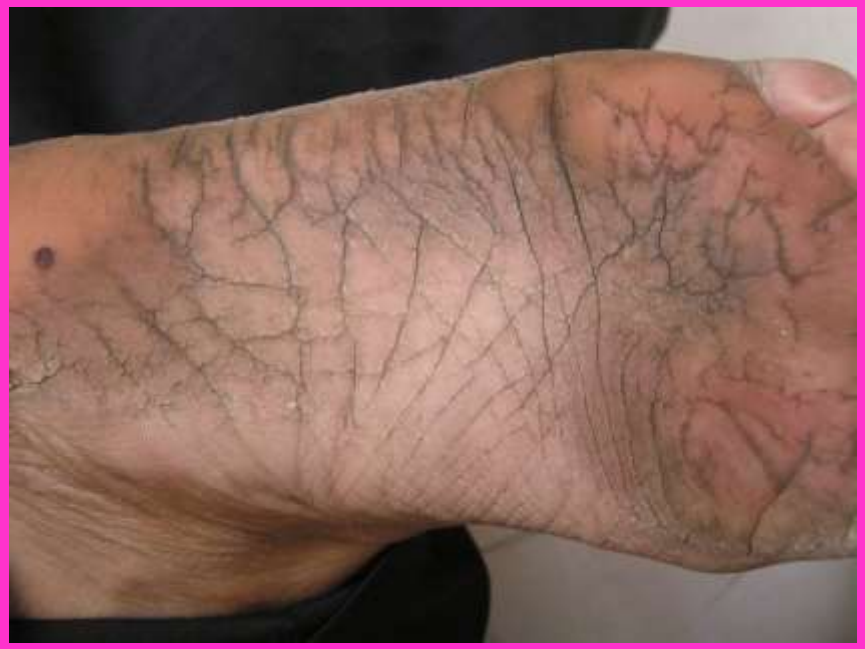
Ichthyoses vulgaris







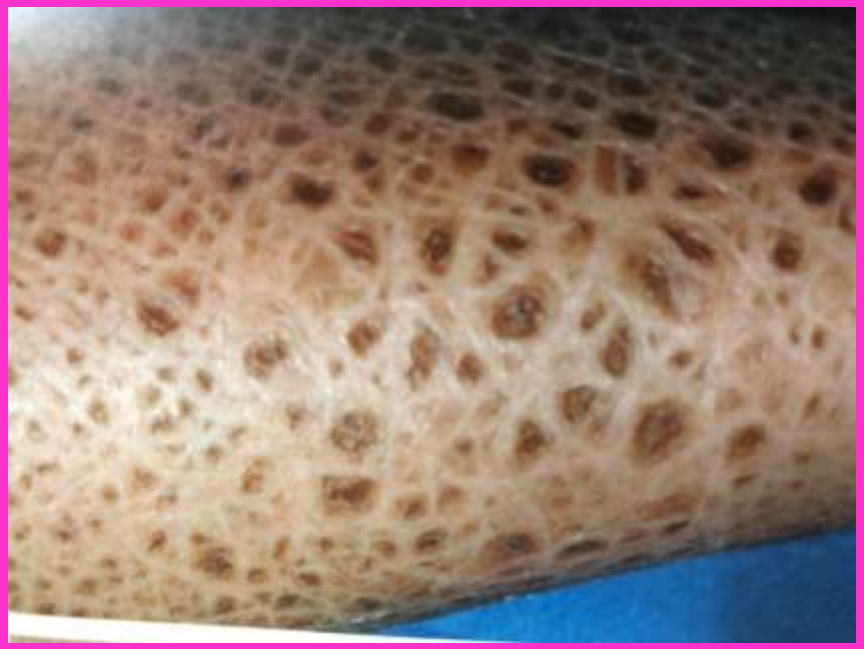
Ichthyoses vulgaris



X linked recessive ichthyoses

- **Xp22.31**deletion→**steroid sulfatase** deficiency
- Hence no Cholesterol sulfate &DHEAS hydrolysis →cholesterol 3 SO4↑↑↑which also inhibits transglutamise 1 (lamellar overlap)
- Pregnancy with affected fetus →no DHEAS hydrolysis →no or low estrogen →no Cx dilation →Caeser in most
- Birth – mild erythroderma & gen. peel →classic dark brown polygonal adherent scales on extremities, trunk & neck (dirty neck)
- Preauricular classic
- Palms, soles, folds & remaining face spared
- Unlike ichthyoses Vulgaris does not improve with age
- Corneal opacities in 10-50% (in female carriers as well)
- Cryptorchidism –testicular CA or hypogonadism

X linked recessive ichthyoses



X linked recessive ichthyoses

- syndromes in 5% (large gene deletion)
  - kallmann (hypogonad+anosmia)
  - ocular albinism
  - intellectual disability
  - short stature
  - autism

Hpe : hyper or para with↑ granular layer

Normal cell turnover and water homeostasis

Δ : genetic (even on chorionic villi or amniotic cells)

↓maternal serum estriol + ↑Non hydrolysed sulfated steroids in urine

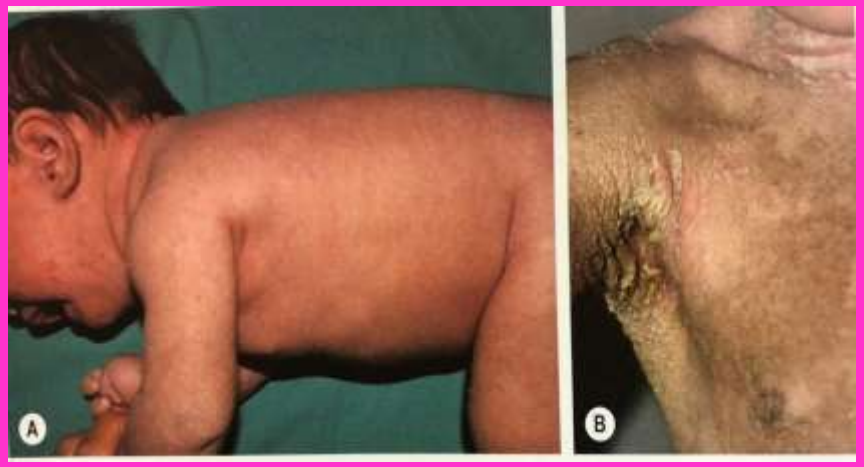
X linked ichthyoses against ichthyoses vulgaris

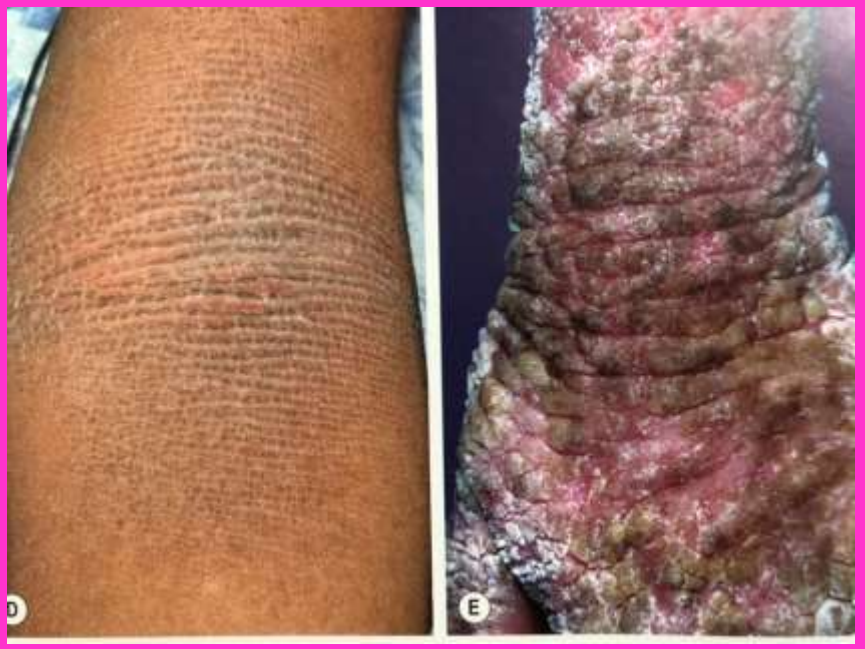
- Dark scales
- No palms and soles
- No KP
- Corneal opacities
- Steroid sulphatase deficiency

Epidermolytic Ichthyosis/hyperkeratosis (BIE)

- AD (50% due to new sporadic mutation)
- **Keratin 1** (severe PPK)& or **keratin 10** (heterozygous)
- Coexpressed in well differentiated spinous & granular
- Weak cytoskeleton due to perturbed keratin alignment→acanthosis, hyperproliferation
- Barrier loss, water loss, sepsis/ bacteria odour
- Birth erythroderma →peeling erosion denuded areas →skin fragility, blister erythema →hyperkeratosis(infancy or later) but periodic shedding and denuded areas ++
- flexures →ridged hyperkeratosis, Ext →cobble stone
- PPK(usually severe)

Epidermolytic Ichthyosis/hyperkeratosis





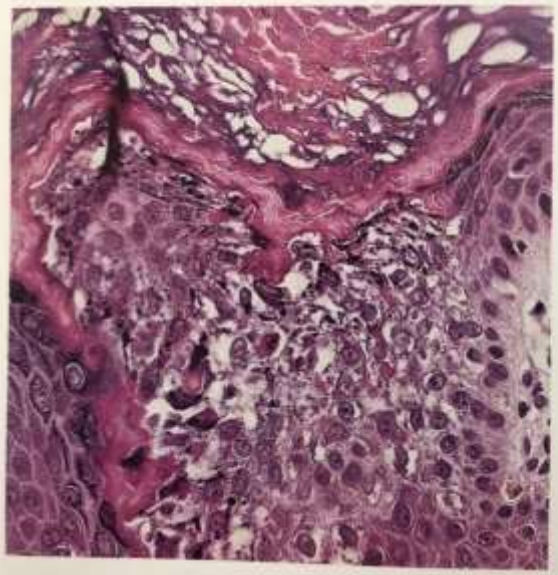


Fig. 57.7 Histology of epidermolytic ichthyosis. Striking ortho-hyperkeratosis, intracellular vacuolization of keratinocytes, and a prominent granular layer with clumped keratin filaments are seen.

Epidermolytic Ichthyosis/hyperkeratosis (BIE)

- **Variants** – cyclical, annular, mosaic (blaschko), ichthyosis hystrix like
- **Hpe**: dense ortho,acanthosis, hypergranulosis, cytolysis (epidermal blisters)

  intracytovacuoles (dense keratin intermediate filament clumps)

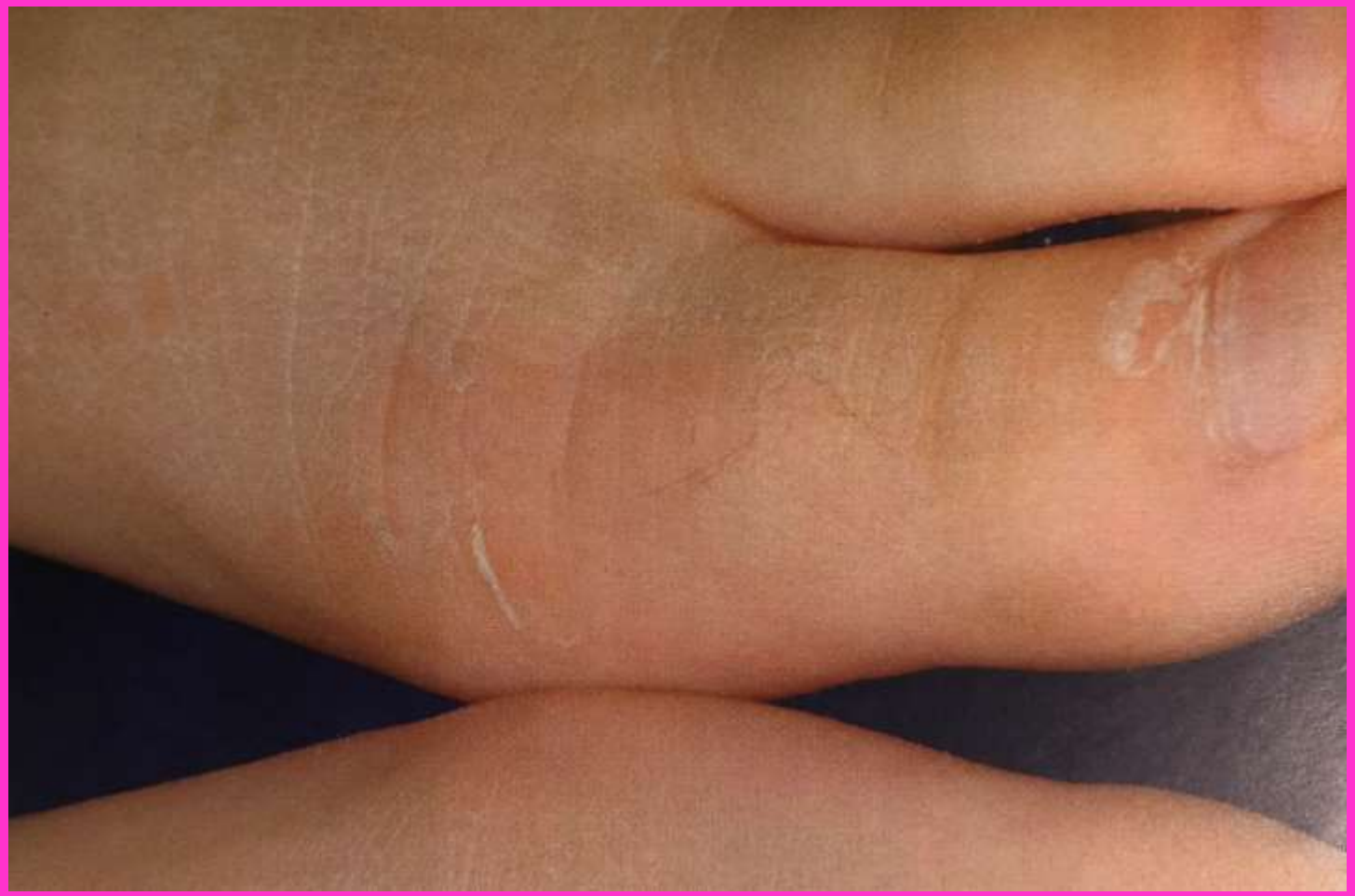
Δ : clinical odour hpe (blistering at birth with focal recurrences and frequent superinfections

Treatment : Emmolients, humectants, antibiotics+ low dose retinoids (may ↑fragility & blisters)

Superficial epidermolytic ichthyoses

- AD
- **KERATIN 2** Gene (exp. Only in spinal & granular)
- "Moulting" or "Mauserang"
- Very mild 'epidermolytic icthyoses'
- Palmoplantar sparing
- Granular layer vacuolization
- Similar to peeling skin syndrome but no vacuoles

Superficial epidermolytic ichthyoses



Ichthyoses with confetti (variegata)

- AD
- Frame shift mutation **K10 or K1** or mosaicism
- Born with Ichthyosiform erythroderma +PPK
- Later 1000s of confetti like islands of normal skin
- Perinuclear vacuolization+

Ichthyoses with confetti (variegata)

Ichthyoses hysterix curth macklin

- Frame shift mutation (mild) **Keratin 1**
- Mimics (EI) –mild to severe-porcupine
- No blister, No skin fragility
- No keratin clump, no epidermolysis
- PPK+

Ichthyosis hysterix (porcupine man)

- Not a clinical entity
- Massive hyperkeratosis with verrucous surface or protruding porcupine like spines
- Seen in
  - -EI
  - -KID (keratitis,I, deafness)
  - -HID (IH deafness)
  - -IH(Curth Macklin)
  - - Verrucous epidermolytic nevi

Ichthyosis hysterix (porcupine man)

Collodion baby

- Not a clinical entity
- Transglutaminase 1 & others
- Premature delivery (↑mortality & morbidity)

→Taut shiny transparent membrane (plastic wrap)

→Ectropion, eclabium, nasal ear cartilage dys.

→Dries cracks breaks fissures & bands---2-4 weeks

→cause seen

Water loss , infection, barrier function problems

Collodion baby

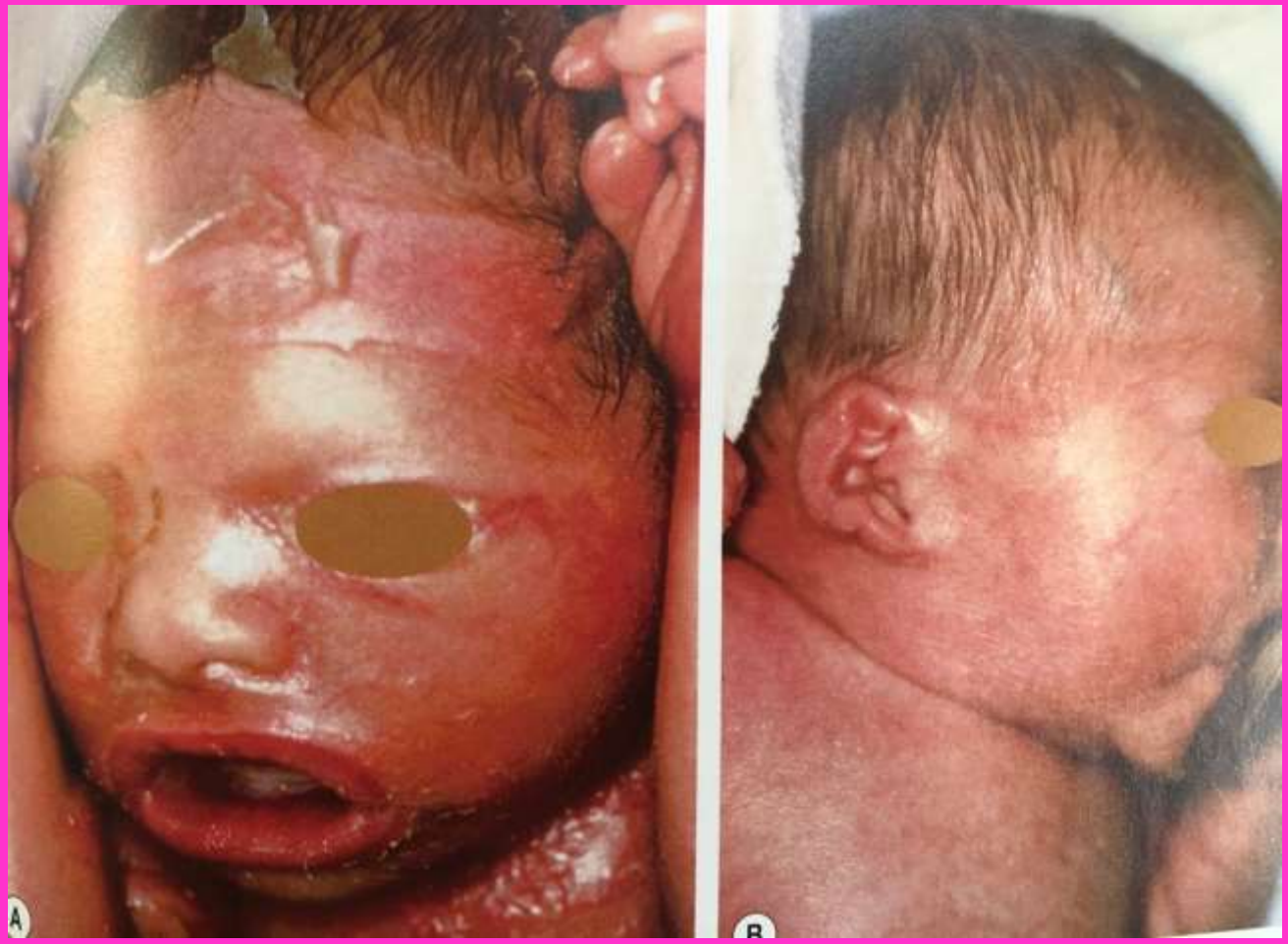
- Lamellar
- NBCIE
- Self healing mild
- Trichothiodystrophy
- Sjogren larson (rare)
- Neutral lipid storage (rare)

causes

Treatment : Thermoinstability, Hypernatremia

Dehydration, Skin infections, sepsis (pneumonia)

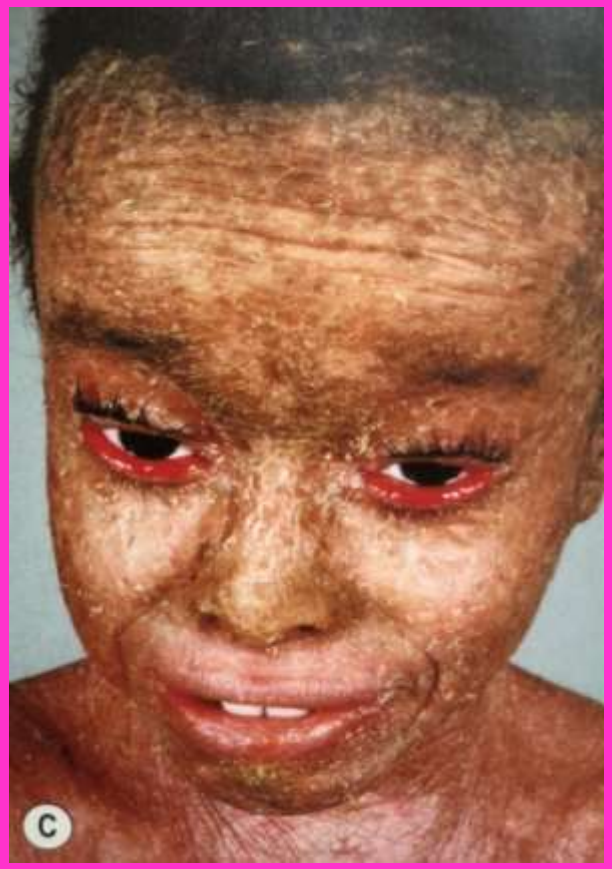
Collodion baby

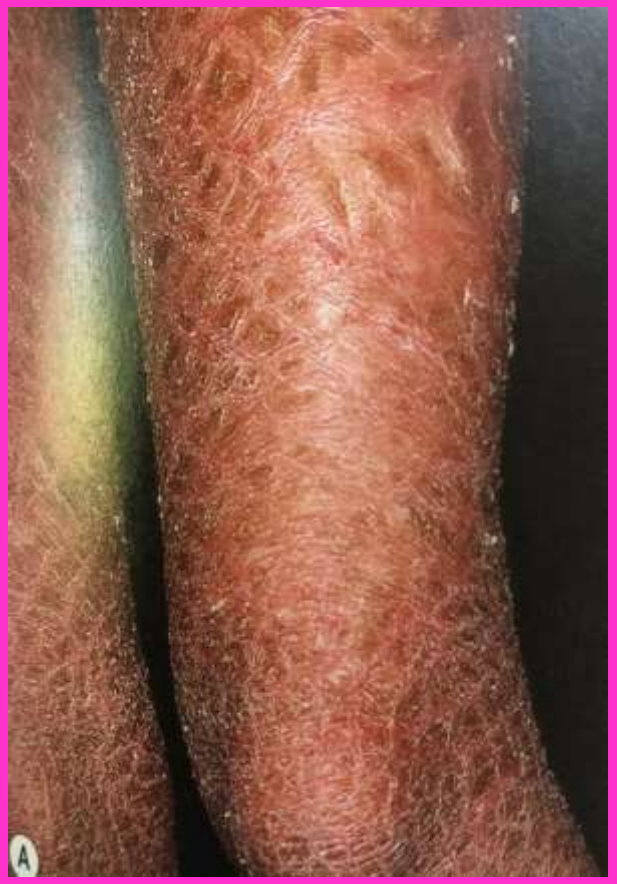


Lamellar ichthyoses (AR) LI

- **Transglutaminase 1** deficiency (mutation in most but not all) **ALOX 12B ,E3, ABCA 12 , CYP4F22**
- Crosslinks various structural proteins to one another as well as to lipid envelope→normal cornification & differentiation.
- Collodion baby (no erythroderma) →large brown plate like scales (bark like pattern)
- Accentuation in flexures & PPK+
- Ectropion, eclabium, nasal ear cartilage dys.

Lamellar ichthyoses

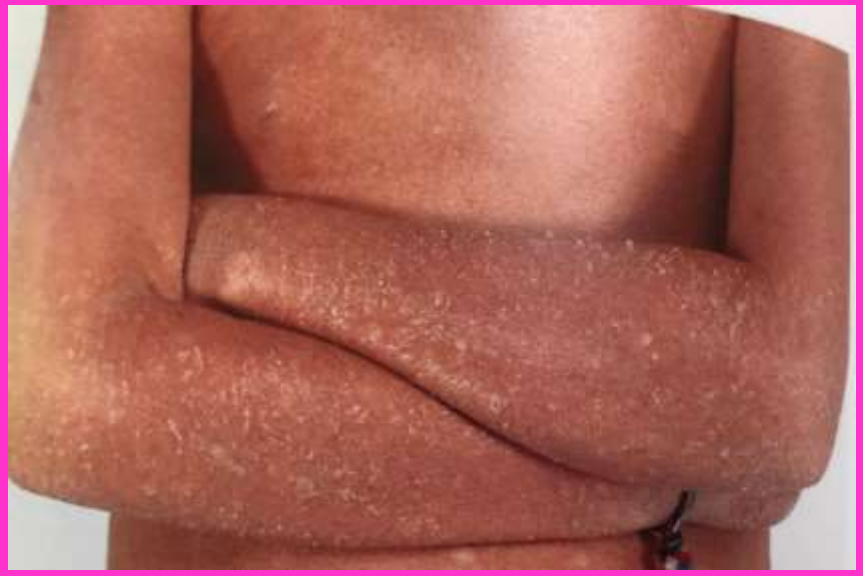




Congenital ichthyosiform erythroderma (Non bullous) CIE

- AR ---9 Gene loci same as **LI**
- Collodion baby→ gen. **Erythroderma** & scaling (throughout life) ---powdery scales
- May mimic with **LI**
- mild to severe variants
- PPK (may be severe)
- ↑ risk of SCC & BCC
- **HPE**:↑Cell turnover, lamellar bodies (lipids) in str corneum
- Retinoids less usefull than in **LI**

Congenital ichthyosiform erythroderma (Non bullous)

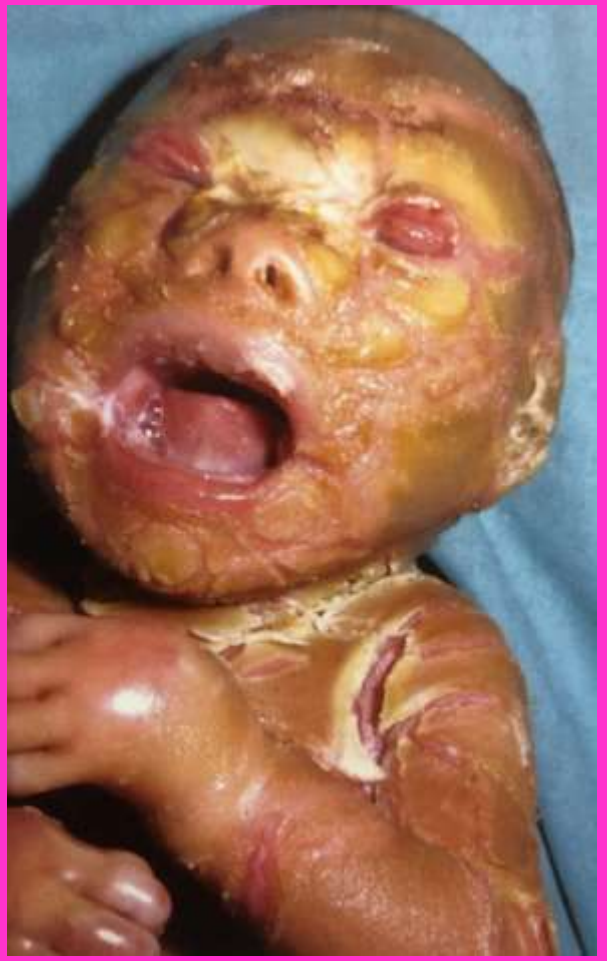


Harlequin (fetus) ichthyosis

- Costume of comic servant character
- **ABCA12**(**A**TP **B**inding **C**asette subfamily **A**)
- Transports ceramides & lipids into lamellar bodies
- No lipid bilayer →massive hyperkeratosis →barrier dysruption
- **KDSR** (3-**K**eto **D**ihydro **S**phingosine **R**eductase) →no ceramide synthesis+thrombocytopenia
- Premature delivery →hard armour like cast (str corneum) →deep red fissures (cracks)+ large yellow adherent plates
- Severe immobilization & ventilation restriction
- Ectropion, eclabium, nasal ear cartilage dys.
- No eyebrows, No eyelashes
- Hand feet mitten like casing
- ↑water & heat loss
- Severe exfoliative ich. Erythroderma+PPK (But most die)

Harlequin (fetus) ichthyosis

- Hpe : perifollicular keratotic material (adnexa plugs)
- Orthokeratosis (missing lamellar bodies & extracellular lipids)
- Retinoids

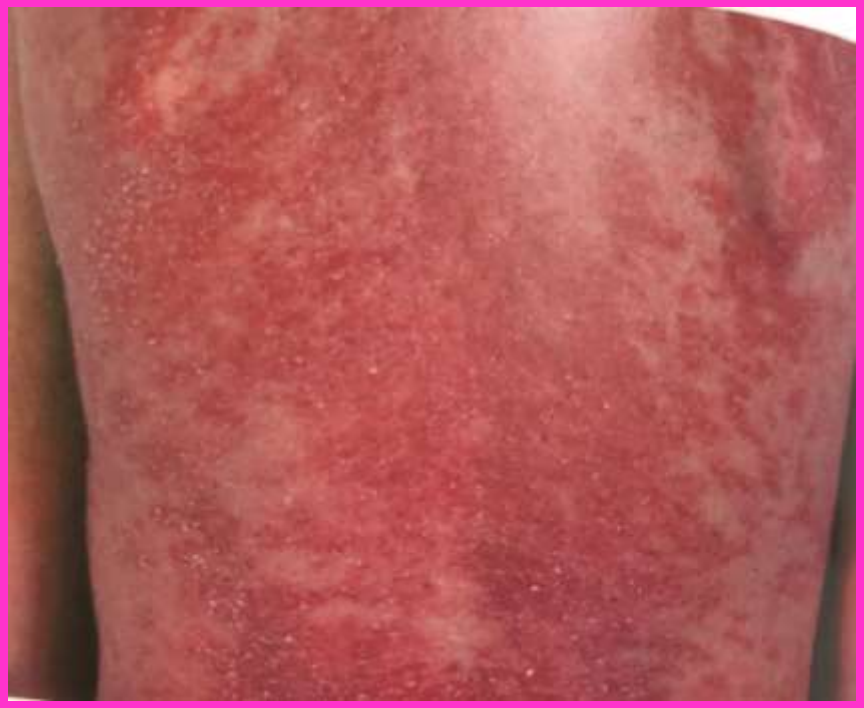


Netherton syndrome (AR)

- **SPINK 5** (Serine protease inhibitor kazal type) gene
- **LEKTI** (lympho-epithelial kazal type related inhibitor) protein → lack →trypsin like proteolytic activity↑↑in str. corneum →disturbed lipid processing enzymes critical for lipid bilayer + desmoglein 1 degradation →shed/dysrupt str.corneum (barrier loss) + antiinflammatory & antimicrobial skin mechanisms lost
- **Skin** : birth **CIE**→ ichthyoses linearis circumflexa (double edge scale)--pruritus ++→eczema /lichenification
- **Hair** : short thin hair of scalp, sparse eyebrow, no eyelashes, bamboo hair (trichorrhexis invaginata) or nodular distal end (golf tee or match stick) + pili torti + trichorrhexis nodosa
- **Immune dysregulation** :

-Atopic	-memory B & NK cells
-IgE↑↑	-HPV, Staph & other sepsis
-Eosinophils ↑↑	-BCC & SCC ↑↑

Netherton syndrome



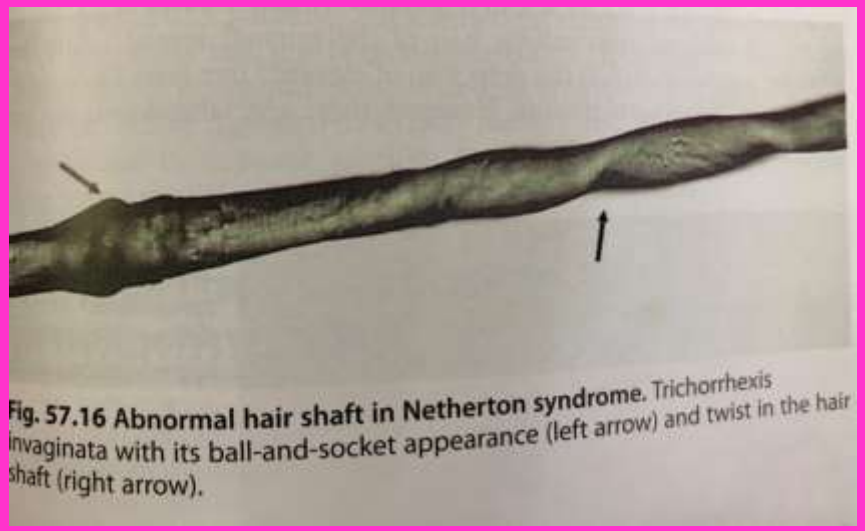
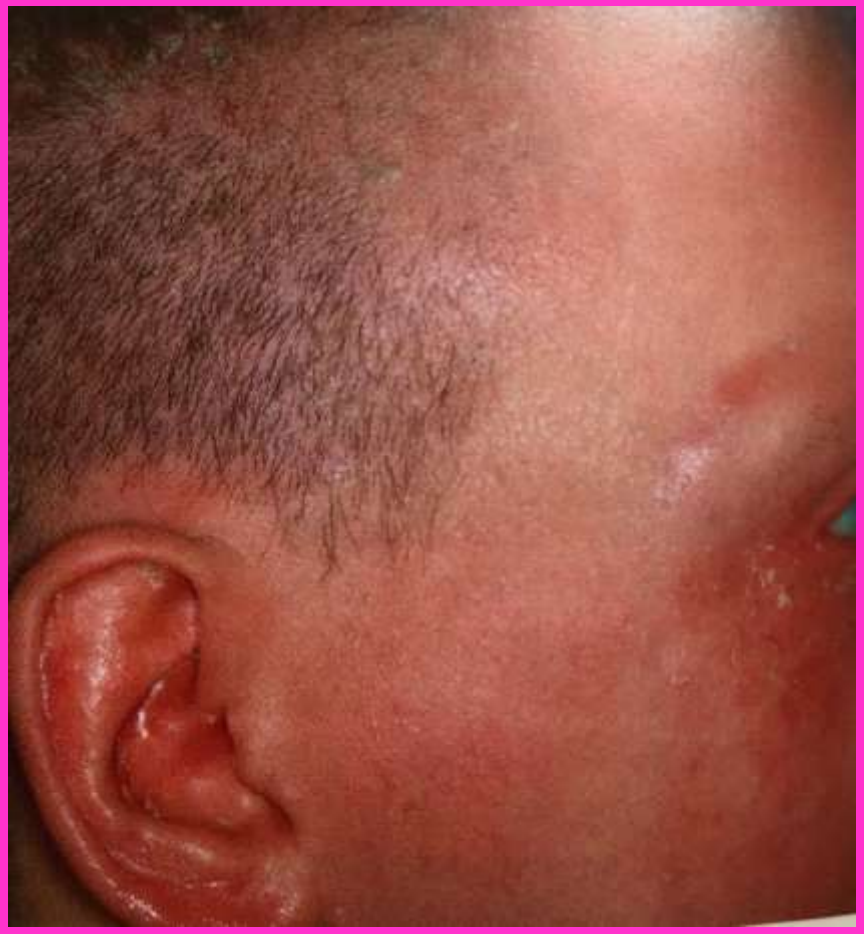
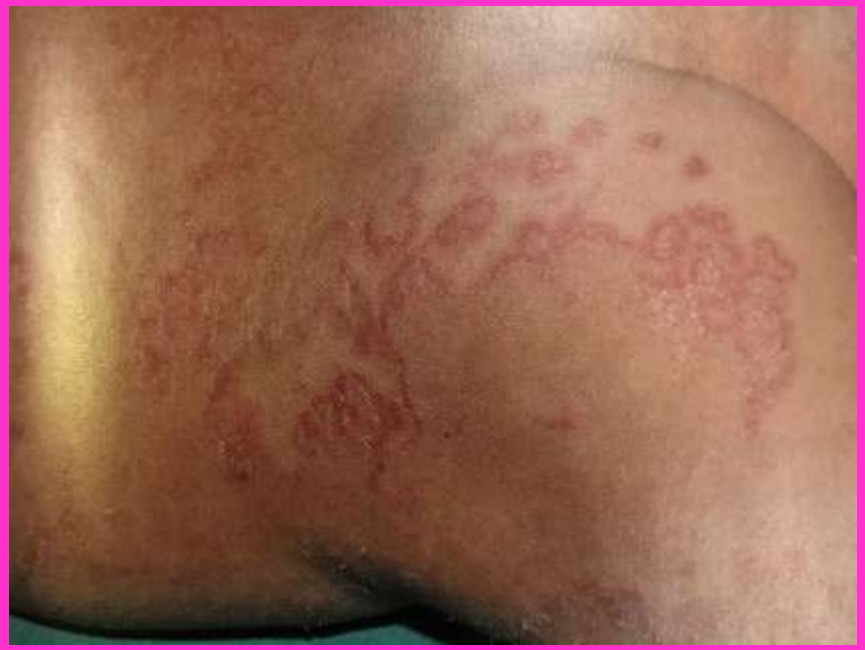


Fig. 57.16 Abnormal hair shaft in Netherton syndrome. Trichorrhexis invaginata with its ball-and-socket appearance (left arrow) and twist in the hair shaft (right arrow).

Netherton syndrome





Netherton syndrome

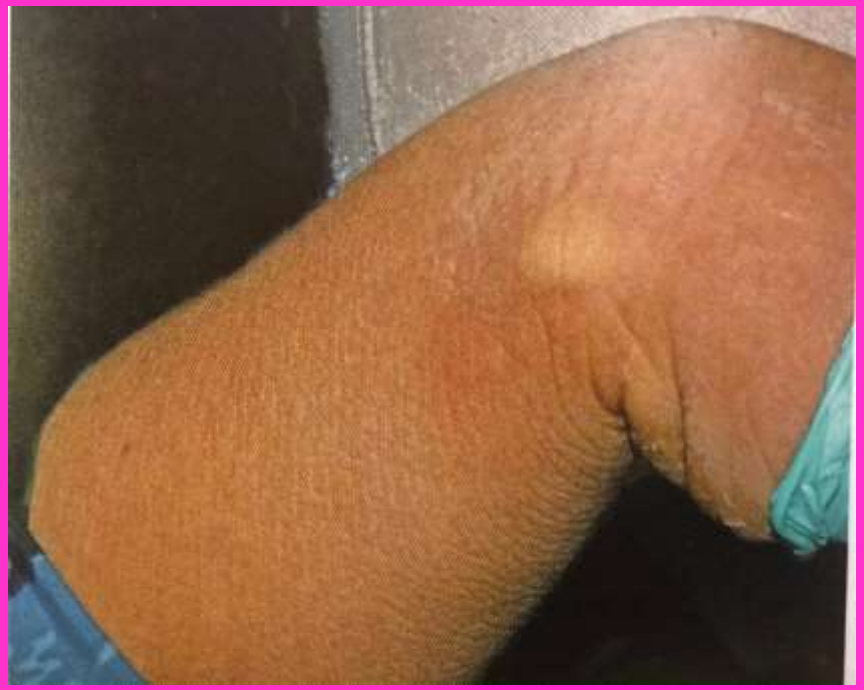
- Hpe : para. Hyperkeratosis, ↓granular layer, acanthosis, band like perivascular (papillary)
- EM-premature lamellar bodies in upper epidermis
- Trichoscopy (in children not infants) and genetics
- DD : - -EKV
  -psoriatic erythroderma,
  -peeling skin syndrome,
  -AD-hyper IgE syndrome,
  -acrodermatitis enteropathica,
  -primary immunodefficiency (wiskot -aldrich)

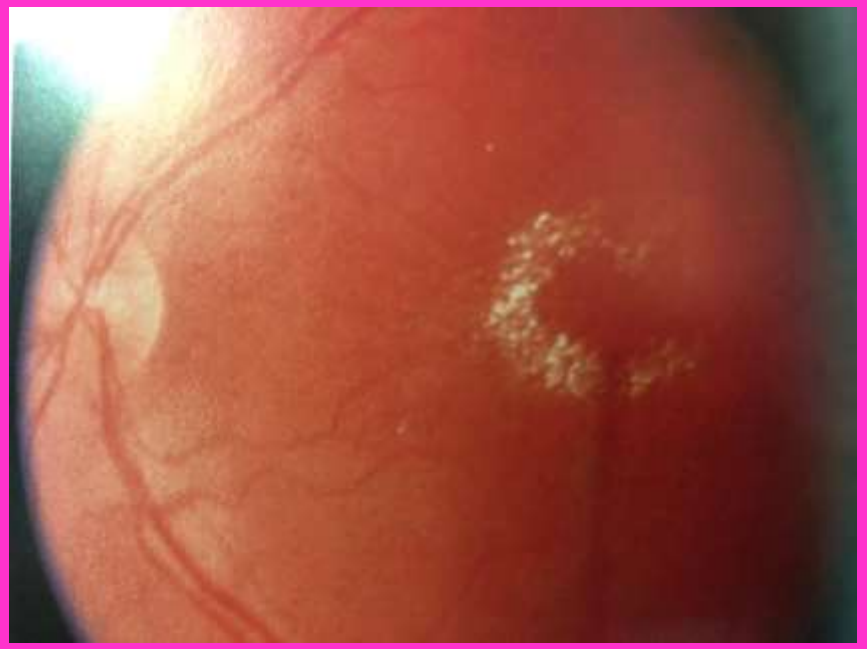
Treatment : emmolients, nutrition, sepsis, retinoids±, NB-UVB

Sjogren Larson syndrome (AR)

- (Gene)**ALDH3A2** → Fatty aldehyde/alcohol dehydrogenase complex →no oxidation of long chain FA & ↑ ↑Fatty alcohol &aldehyde modified proteins & fats
- Complex imp. in epidermal ceramide recycle & glycerolipids / sphingolipids catabolism →retarted /dysmyelination
- Also role in LTB4 degrade & AA metabolism (pruritus)
- Birth –hyperkeratosis, erythema (fades later) & scaling which →prominent & dark or variable severity later
- Accentuation in abdomen , neck & flexures
- No ectropion, eclabium, alopecia
- PPK+
- PRURITUS+→Lichenification
- Perifoveal glistening white dots (mac. dystrophy)---Δtic

Sjogren Larson syndrome





Sjogren Larson syndrome

CNS features start at the end of one year

- **di / tetraplegia** (LL>UL)
- -delayed motor
- -seizures
- -spasticity & contractures
- **Mental retardation**
- -pyramidal signs
- -hypertelorism
- -speech defects

Δ : FALDH activity in fibroblasts, wbcs, epidermis

↑ levels of FF alcohols (plasma)

fundoscopy & genetics

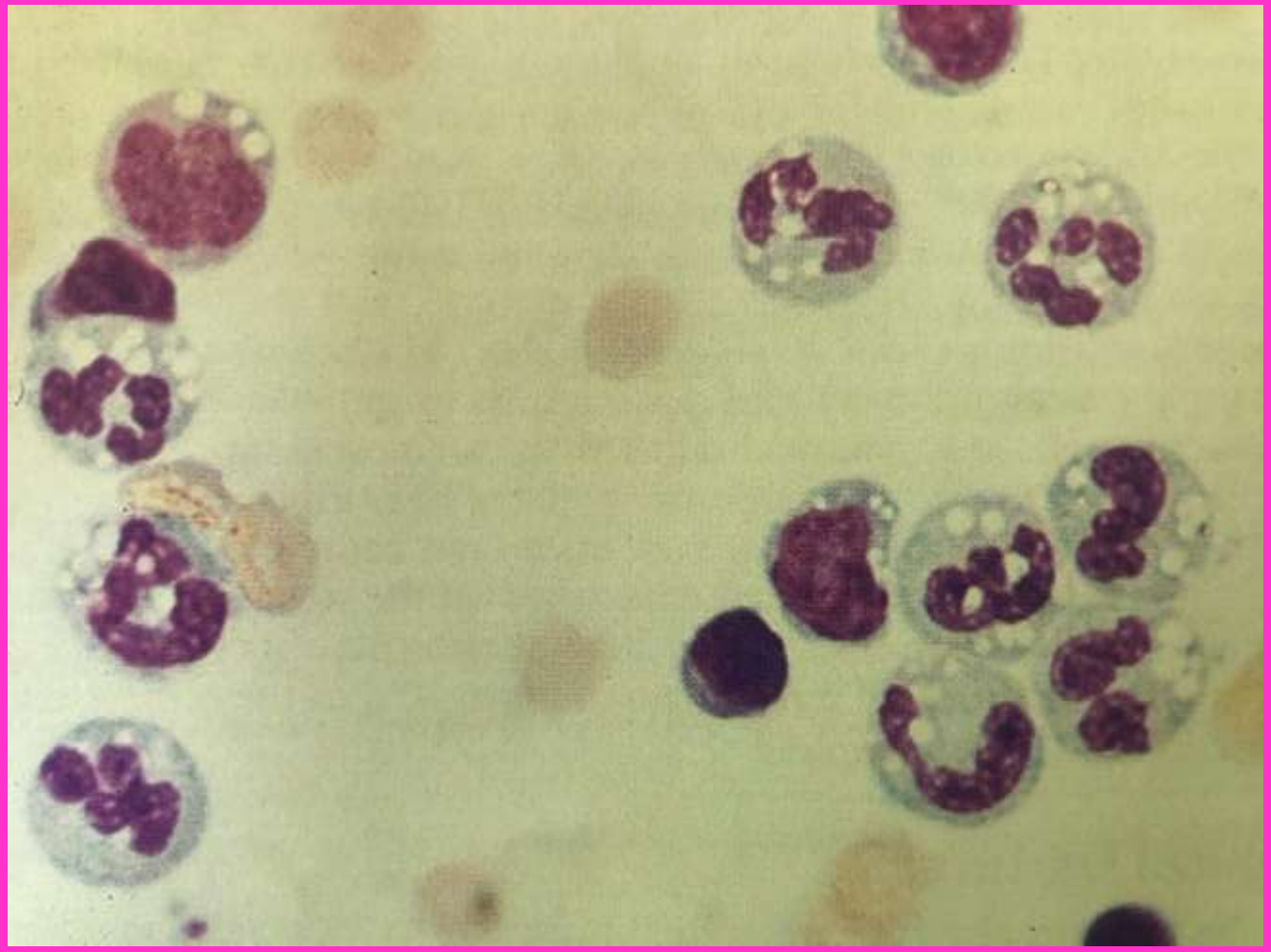
Treatment : Low dose retinoids

5-lipooxygenase inhibitors(blocks LTB4)→pruritus↓ (zileuton)

Chanarin dorfman syndrome (AR)

- Neutral lipid storage disease (↑Tgin cyto.) with ichthyoses
- **ABHD5**→Activator of adipose Tg. Lipase (**ADGL**) →no triglycerol hydrolysis →↑↑↑**Triglycerides**
- At birth **CIE** →generalised scaling & erythema
- Hepatomegaly (fatty degeneration & fibrosis)
- Myopathy
- Cataracts, SN deafness, develop delay
- Δ : fresh PBS- lipid containing vacuoles in circulating granulocytes & monocytes but not in lymphocytes or eosinophils (Jordans anomaly)
- DD: refsum →not cong & ich. Vulgaris (skin)

Chanarin dorfman syndrome



Trichothiodystropy with ichthyoses

Photosensitivity, I, Brittle hair Infertility, Develop delay, Short stature

- Heterogenous group , neuroectodermal
- General transcription factor (**TFIIH**) ----photo
- **ERCC2/XPD, ERCC3/XPB , GTF2H5** genes—subunits of (TFIIH)
- **MDLKIP** (Regulates mitosis & cytokinesis) ----non photo
- **X-linked RNF113 A** (tumour suppression & DNA repair)
- **Skin** : birth **CIE**→ variable scaling →ichthyoses vulgaris, photosensitivity in 50%
- **Hair** : short ,unruly, fragile hair (low sulphur content) →tiger tail hair (polarising light micro.)
- **Neuro** : ataxia, microcephaly, spastic paralysis etc.
- **No malignancy risk**

Prenatal diagnosis

- **X linked-**---steroid sulphatase levels in amniotic cells
- **BIE**---abnormal morphology of amniotic cells
- **Refsum** ---phytanic acid oxidation in cultured cells
- **Harlequin +BIE+ Sjogren Larson**---

  fetal skin biopsy (precocious keratinization < 24 wks)

Thank you

Treatment

Erythrokeratodermas