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ISBN 978-3-031-60787-5 ISBN 978-3-031-60788-2 (eBook)
https://doi.org/10.1007/978-3-031-60788-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The fast-moving world of genetic research inspired us to present an atlas containing common and rare genodermatoses. It provides the dermatologists, pediatricians, and internists with about 1000 photos of more than 200 different genodermatoses collected from multicenter medical institutions in Egypt since 2010, some of which very rare.

Consanguinity is high in Egypt; hence, many different varieties of genodermatoses with different presentations are encountered. In this atlas, the reader is presented with photos of affected family members at different ages.

The diagnosis of genodermatoses is not an easy task; key points for a correct diagnosis of each disease are mentioned in a concise manner, while a wealth of photographs will assist the practitioner's review, through their colorful presentation, in giving the most accurate diagnosis of the different genodermatoses and counseling families and patients.

With the advances in genetic studies, further research will be of invaluable support to those studying the expected affected gene, to build what may be the basis of gene therapy.

It is the hope of the authoring team that this atlas will, in the meantime, contribute to a better understanding of genodermatoses, their variability, and thus to sound medical decisions and safer, more effective treatments for patients facing a life with these complex conditions.

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Acknowledgments

We would like to thank all the co-authors who contributed to writing the main criteria of the genodermatoses published in this atlas and to the revision of its chapters.

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We would like to thank all the dermatologists who contributed clinical photographs of their patients to this atlas, after obtaining their parents' consent for publication, and who assisted in preparing the chapters.

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Lastly, we would like to thank the Springer team, especially Mrs. Juliette R. Kleemann and Ms. Sharon Spears for their great support during the preparation of this atlas.

Contents

Ichthyoses and Ichthyotic Syndromes

1

Ichthyosis is commonly inherited as a single entity. However, it may be part of syndromes that induce abnormalities in organs other than the skin. These include KID, HID, Chanarin-Dorfman, Refsum, Sjögren-Larsson, Netherton, Tay-Sachs (PIBIDS), Rud's, Laurence-Moon-Bardet-Biedl, MEDNIK, Conradi-Hünermann-Happle, and CHILD syndrome.

1. **Hereditary (Primary) Ichthyoses**
   (a) Common Ichthyoses
   - Ichthyosis Vulgaris
   - X-linked Recessive (XLR) Ichthyosis

   (b) Autosomal Recessive (AR) Ichthyoses
   Major Forms
   - Non-Bullous Congenital Ichthyosiform Erythroderma.
   - Lamellar Ichthyosis
   - Harlequin Ichthyosis

   Minor Forms
   - Self-healing Collodion Baby
   - Acral self-healing Collodion Baby
   - Bathing-suit Ichthyosis

   (c) Keratinopathic Ichthyoses
   - Epidermolytic Ichthyosis
   - Superficial Epidermolytic Ichthyosis (of Siemens)
   - Ichthyosis Hystrix Curth-Macklin
   - Ichthyosis en Confetti

2. **Ichthyosiform Syndromes**
   (a) KID Syndrome
   (b) HID Syndrome
   (c) Chanarin-Dorfman Syndrome
   (d) Refsum Syndrome
   (e) Sjögren-Larsson Syndrome
   (f) Netherton Syndrome
   (g) Tay-Sachs Syndrome (PIBIDS)
   (h) Rud's Syndrome
   (i) Laurence-Moon-Bardet-Biedl Syndrome
   (j) MEDNIK Syndrome
   (k) Conradi-Hünermann-Happle Syndrome
   (l) CHILD Syndrome

Hereditary (Primary) Ichthyosis

Common Ichthyosis

Ichthyosis Vulgaris (AD) [1, 2] (Figs. 1.1, 1.2, and 1.3)

- The most common disorder of cornification.
- Autosomal dominant inheritance: mild ichthyosis with a heterozygous filaggrin (*FLG*) mutation and more severe ichthyosis with mutations in both *FLG* alleles.
- Onset: during infancy and most patients exhibit clear clinical manifestations by the age of 5 years.
- Clinical characteristics:
  - Skin: dry, fine, small, white, flaky scales. The extensor surfaces of the upper and lower extremities are the initial target with sparing of the flexural creases.
  - In most cases, no extracutaneous involvement of the eyes, ears, skeletal, and the nervous systems.
- Associations:
  - Atopic dermatitis, asthma, allergic rhinitis.
  - Palmoplantar hyperlinearity and hyperkeratosis (keratosis punctata).
  - Keratosis pilaris and furrowed heels.
- Prognosis: improves with age and summer.
- Treatment: emollients, humectants, and keratolytics (e.g., urea, lactic, and salicylic acids); the latter group may be irritating in patients with coexistent atopic dermatitis.

X-Linked Recessive Ichthyosis [3] (Figs. 1.4 and 1.5)

- Absence of steroid sulfatase (STS) activity due to the deletion of the entire *STS* gene.
- Almost exclusively affects boys and men, with transmission by asymptomatic female carriers.
- Onset: skin findings usually appear within the first year of life, 15–20% have manifestations at birth.
- Clinical characteristics:
  - Widespread polygonal large dark brown plate-like adherent scales on the anterior aspect of lower legs and trunk with fine-scale on the scalp.

N. Moftah et al., *Atlas of Common and Rare Genodermatoses*, https://doi.org/10.1007/978-3-031-60788-2_1

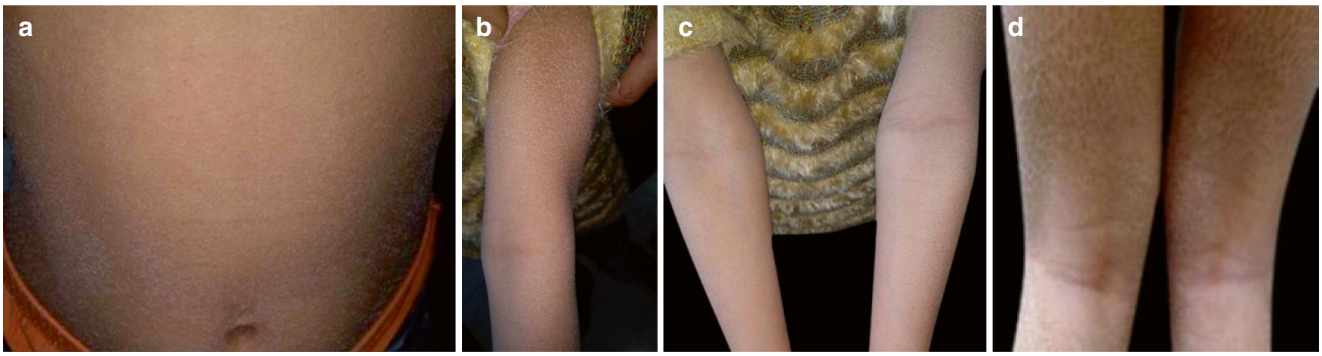

Fig. 1.1 Ichthyosis vulgaris. Fine white scales on the abdomen (**a**) on the limbs (**b**, **c**, **d**), sparing flexures (**c**, **d**)

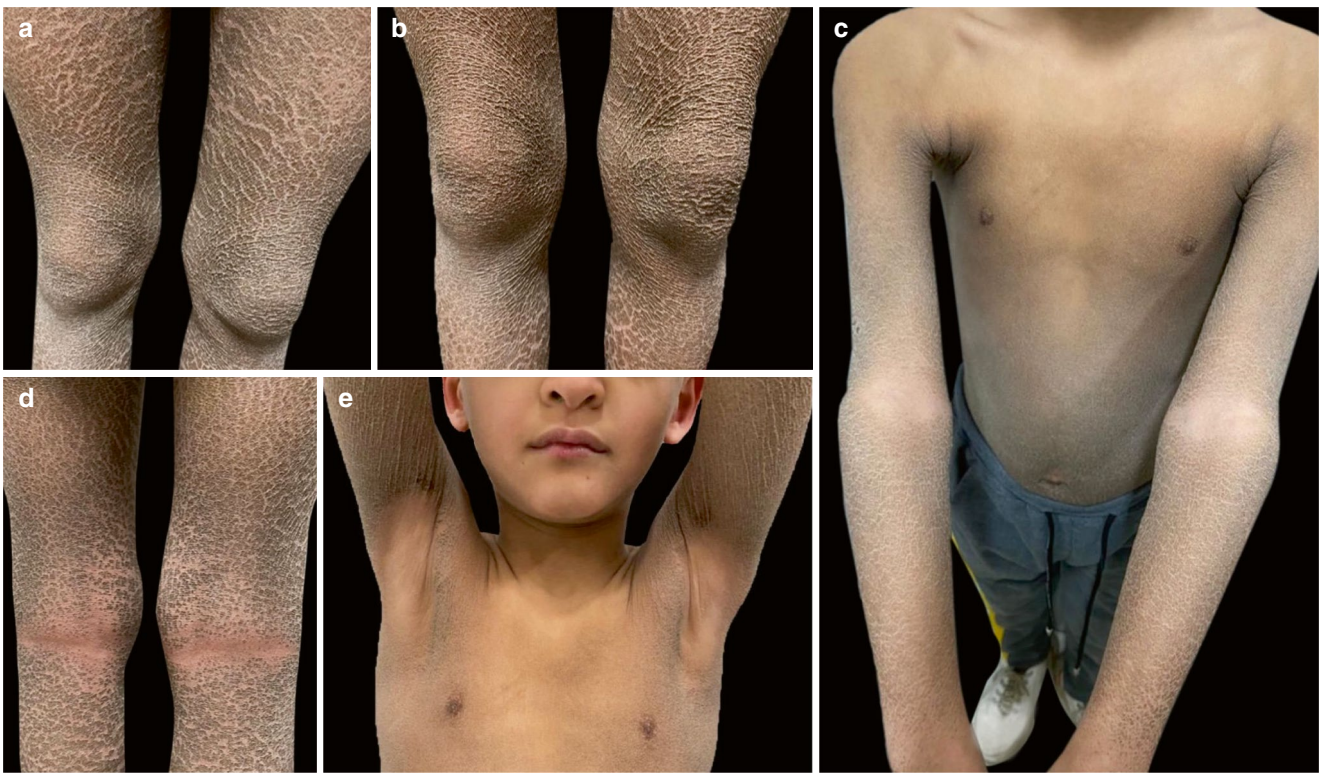

Fig. 1.2 Ichthyosis vulgaris. Large adherent scales, grayish tessellated (tile-like), similar to fish skin on the lower legs (**a**, **b**), sparing flexures (**c**–**e**)

  - Dirty neck appearance and affection of axillae.
  - Face (except pre-auricles), palms, and soles are spared. Flexor areas are variably involved.
- Associations:
  - Corneal opacities.
  - Cryptorchidism.
  - Prolonged labor due to low placental estrogen production (may result in birth via cesarean section).
- Prognosis: improves with summer, worsens with age.
- Treatment: topical humectants, keratolytics, and retinoids.

Autosomal Recessive (AR) Ichthyoses

Non-Bullous Congenital Ichthyosiform Erythroderma (AR) [4] (Figs. 1.6 and 1.7)

- Mutations in Transglutaminase 1 (*TGM1*), *ALOXE3*, *ALOX12B*, and *NIPAL4* genes.
- Onset: at birth.
- Clinical Characteristics:
  - Scales: at birth with collodion membrane, generalized erythroderma with fine, flaky white, powdery scales. Flexures, face, palms, and soles are involved.

Fig. 1.3 Ichthyosis vulgaris. Hyperlinearity of the palms (accentuated skin marking) (**a**), dorsum of feet (**b**), knees (**c**)

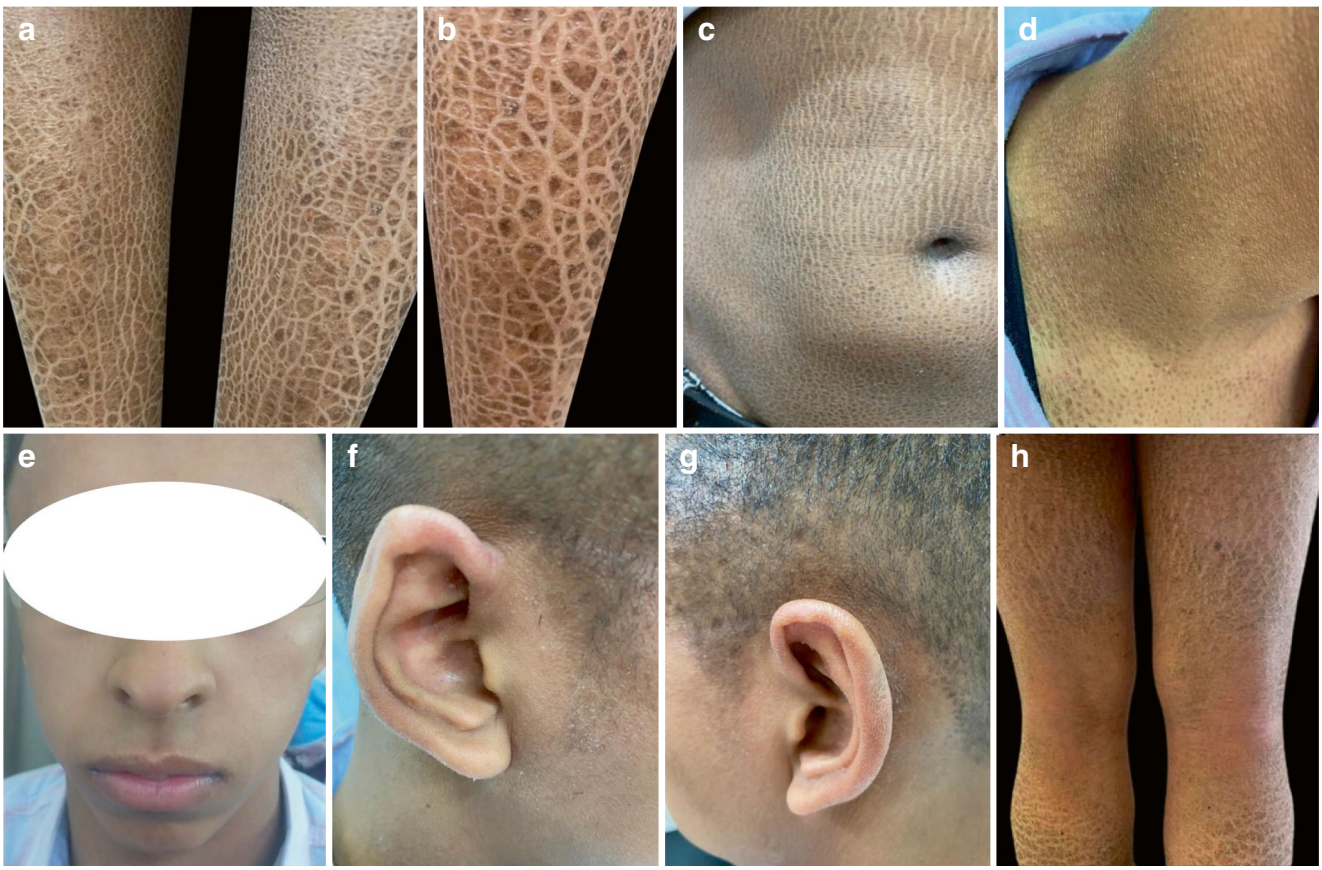

Fig. 1.4 X-linked ichthyosis. Large prominent dark dirty brown scales on limbs (**a**, **b**) smaller light brown on trunk (**c**), Dark scales on the neck 'dirty neck' (**d**), face spare (except pre-auricles) (**e**–**g**), with sparing flexures (**h**)

  - Mild form of lamellar ichthyosis.
  - Hearing impairment due to accumulation of scales in external ear ± scarring alopecia.
  - Hyperkeratotic lesions on joints.
  - Ectropion, palmoplantar hyperkeratosis, heat intolerance, and hypohidrosis due to obstruction of sweat ducts and nail dystrophy may occur.
  - Severe exfoliative erythroderma may cause metabolic stress or mild growth retardation.
- Treatment: oral retinoids are more beneficial for scaling than for the associated erythema; increased intake of fluids, calories, and protein is required for erythrodermic patients.

Lamellar Ichthyosis (AR) [5, 6] (Figs. 1.8, 1.9, 1.10, 1.11 and 1.12)

- Mutation in *TGM-1* and *ABCA12* genes.
- Onset: at birth.
- Clinical Characteristics:
  - Usually a collodion-like membrane is present at birth.
  - During the first week of life, the membrane cracks and peels off in sheets then forms generalized large thick,

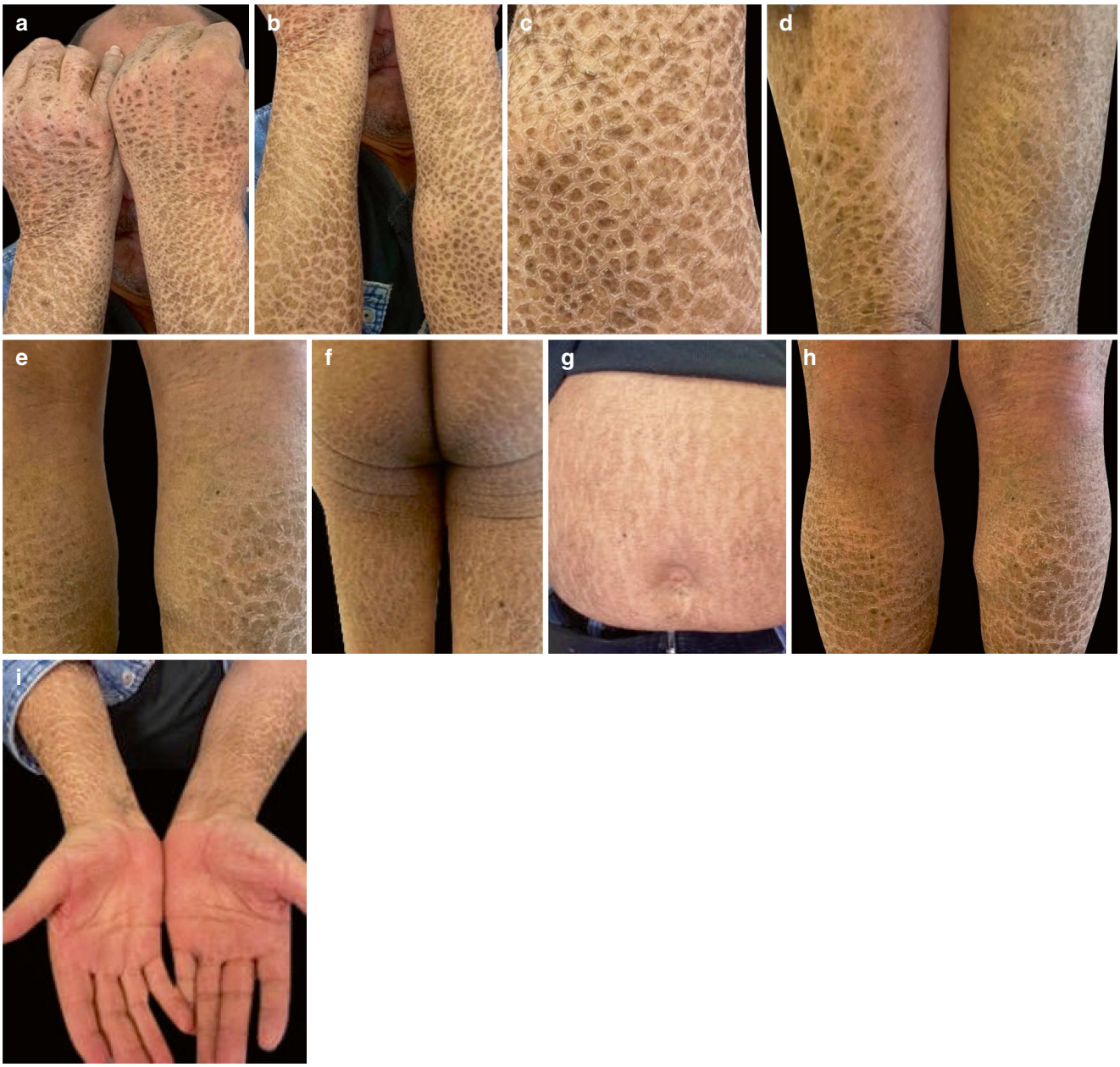

Fig. 1.5 X-linked ichthyosis in adult male. Large prominent dark dirty brown scales on upper limbs (**a**–**c**), lower limbs (**d**, **e**), buttocks (**f**), abdomen (**g**). Flexor areas and palms are spared (**h**, **i**)

dark, brown plate-like adherent scales, which are quadrilateral, adherent in the center, and free at the edge with raised border often leading to superficial fissures, forming a mosaic or bark-like pattern. Erythroderma is either absent or minimal.

- Heat intolerance (heat stroke) and hypernatremia.
- Scarring alopecia especially at the periphery of the scalp (tautness of facial skin) and sparse scalp hair.
- Marked ectropion due to taut skin as well as plate-like scales around eyes associated with madarosis, conjunctivitis and keratitis, eclabium, hypoplasia of nasal and auricular cartilage (crumbled).
- Ears are small and deformed. Accumulation of scales in the ear may lead to recurrent infection.
- "Bathing-suit ichthyosis" caused by temperature sensitive *TGM-1* mutation affects primarily trunk and scalp with a higher incidence in the South African population.
- Palmoplantar hyperkeratosis range from accentuating skin markings to severe thickened skin with cracking and fissuring.
- Hypotrichosis and nail dystrophy with thickening and ridging.
- Prognosis: persistent.

Fig. 1.6 Non-Bullous congenital ichthyosiform erythroderma. Generalized Fine, flaky white, powdery scales with dry skin and persistent generalized erythroderma on face with ear affection (**a**, **b**), back (**c**), limbs with flexures (**d**, **e**), and palmoplantar hyperkeratosis (**f**, **g**)

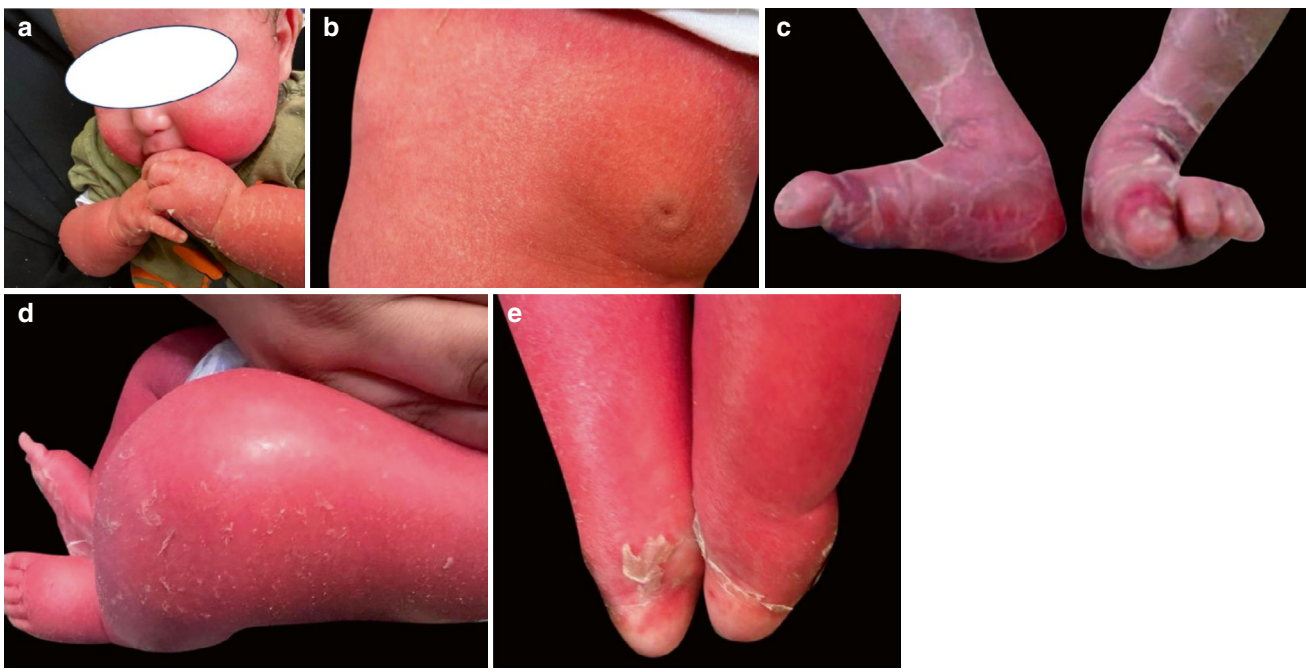

Fig. 1.7 Non-bullous congenital ichthyosiform erythroderma. Generalized fine, flaky white, powdery scales with dry skin and persistent generalized erythroderma on face (**a**), trunk(**b**) and limbs (**c**–**e**)

Fig. 1.8 Lamellar ichthyosis. 2 weeks neonate with large, plate-like scales on face (taut skin causing ectropion), scalp, ear deformity and accumulation of scales in the ear (**a**–**c**), limbs and extremities (**d**, **e**)

- Treatment: acitretin use during early childhood is effective for hyperkeratosis and scaling. Acitretin improves ectropion and avoid eye complications and eyelid surgery.

Harlequin Ichthyosis (AR) [7, 8] (Figs. 1.13 and 1.14)

- Mutation in *ABCA12* gene.
- It is a severe and usually fatal form of ichthyosis.
- Onset: infant born premature.
- Tightly encased neonate.
- Encasement of hard thickened stratum corneum leads to hyperkeratotic cast (cracks).
- Scales: large, yellow, brown adherent plate, separated by broad deep intensely red fissures gives armor-like plaques. Baby is stillborn or dies soon after delivery. Acitretin may allow survival, with treatment may develop into lamellar ichthyosis or congenital ichthyosiform erythroderma-like phenotype.
- Complications in the neonatal period:
  - Tautness of facial skin with severe ectropion.
  - Eclabium and microcephaly.
  - Flat ears, rudimentary or absent, and deformities of the nose (all with taut skin lead to grotesque appearance and distortion).
  - Hands and feet are edematous and swollen leading to mitten hands and feet.
  - Autoamputation.
  - Eyelashes/eyebrows are usually missing (spare scalp hair).
  - Erythroderma.

Fig. 1.9 Lamellar ichthyosis. Female patient with large, plate- like scales on face with obvious ectropion, scarring alopecia with ear deformity and accumulation of scales in ear (recurrent infection) (**a**–**c**), plate-like scales with mosaic pattern on trunk (**d**), upper limb and extremities (**e**, **f**). Hyperkeratosis of the palms and nail dystrophy (**f**, **g**)

Fig. 1.10 Lamellar ichthyosis. A male patient with large, plate-like scales on face with ectropion, scarring alopecia, eclabium (**a**). Large thick, dark plate-like adherent scales in the center and free at the edge and form a mosaic pattern (reptilian scales) on trunk (**b**, **c**), limbs and extremities (**d**–**f**). Hyperkeratosis of the soles (**g**)

  - Dies within days due to respiratory failure and sepsis.
  - Taut facial skin prevents the infant from suckling.
- Treatment: systemic retinoid and advanced neonatal intensive care (life-threatening and often fatal disorder).

Collodion Baby (AR) [9] (Figs. 1.15 and 1.16)

- Onset: these babies are often premature with low birth weight.
- Born covered with a taut, yellow, shiny, transparent membrane resembling plastic wrap, a cellophane-like membrane. Within 2–3 weeks, the membrane peels off in sheets, leading to erythema, mild scaling, ectropion, eclabium, and distortion of nose and ears (misshapen or crumbled ears), hypoplastic fingers, nose, and anonychia.
- Complications: impaired suckling, restricted ventilation, fluid and electrolyte imbalances, dehydration, skin infection, and sepsis.
- Prognosis:
  - Collodion baby is the usual presentation for Harlequin ichthyosis and congenital ichthyosiform erythroderma. AD lamellar ichthyosis, Sjögren-Larsson syndrome, trichothiodystrophy, neutral lipid storage disease, Conradi-Hünermann-Happle syndrome, Hays-Wells syndrome, and ectodermal dysplasia may also occasionally present as collodion baby.
  - A subset of collodion babies with underlying mutations in *TGM1, ALOX12B*, or *ALOXE3* have a "self-healing" phenotype (self-healing collodion baby) where the skin is fairly normal in appearance when the membrane resolves.
- Treatment: humidified incubator, emollients, and monitoring for complications; keratolytics and manual debridement of the membrane are not advised due to risk of systemic absorption and infection, respectively.

Fig. 1.11 Lamellar ichthyosis. Large thick brown plate-like scales on face with obvious ectropion, scarring alopecia (periphery of scalp) (**a**). Large, plate-like scales forming a mosaic pattern on trunk (**b**, **c**), scalp (**d**), and limbs with significant flexural involvement (**e**–**g**)

Fig. 1.12 Lamellar ichthyosis in an adult female. Adult patient with obvious ectropion with large, plate-like scales on face, scarring alopecia with ear deformity (**a**–c). Large, plate-like scales forming a mosaic pattern on neck, trunk, limbs, extremities (**c**–**f**), and palmar hyperkeratosis (**g**)

Fig. 1.13 Harlequin Ichthyosis. Obvious ectropion with large, yellow, horny, extremely thickened armor-like plaques on face associated with eclabium and scarring alopecia (**a**), mitten hands and feet (**b**, **c**)

Fig. 1.14 Harlequin Ichthyosis. Eclabium and obvious ectropion with extremely thickened scales with red deep fissures on face, neck, upper chest (**a**, **b**) and lower trunk (**c**)

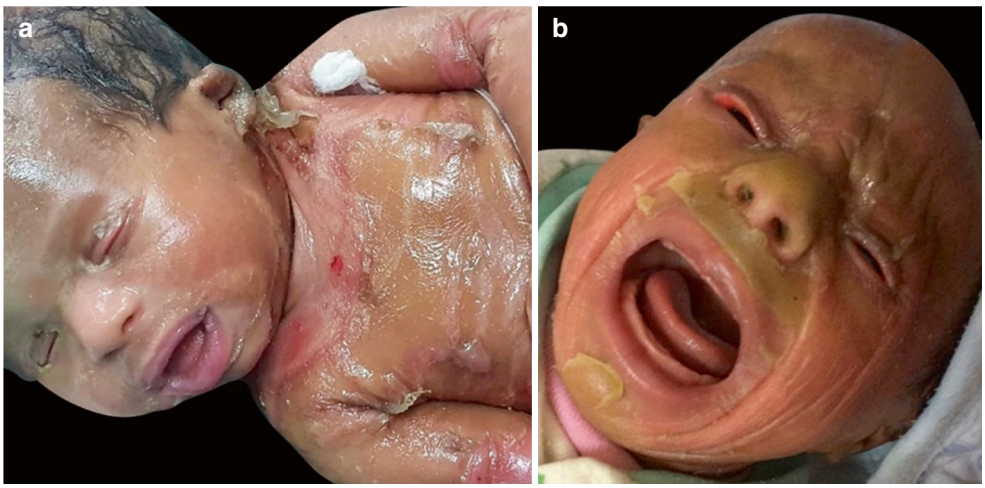

Fig. 1.15 Collodion baby. Day 1 with shiny, transparent membrane resembling plastic wrap, ectropion, eclabium with deformed ears (**a**). Day 5 with erythema, diffuse mild scaling, ectropion, eclabium (**b**)

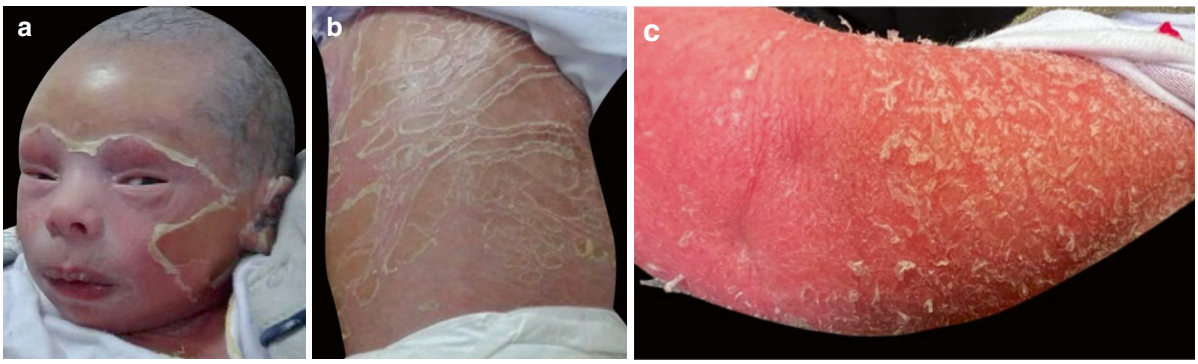

Fig. 1.16 Collodion baby. Baby with a taut, shiny, transparent membrane resembling plastic wrap with erythema on desquamation (**a**–c)

Keratinopathic Ichthyoses

Epidermolytic Ichthyosis (AD) [10] (Bullous Congenital Ichthyosiform Erythroderma) (Multiple-Ridged Hyperkeratosis) (Figs. 1.17, 1.18, 1.19, and 1.20)

- Mutation in Keratin *(KRT1)* gene is associated with severe palmoplantar hyperkeratosis while mutation in *KRT10* spare palms and soles.
- Onset: at birth.
- Clinical characteristics:
  - Erythroderma, peeling, erosions, denuded skin, and multiple blisters (misdiagnosed as epidermolysis bullosa in newborns).
  - Later (First few months): decrease skin fragility, with the development of widespread erythema, hyperkeratosis, and focal erosions that form yellow-brown, thick, warty, corrugated ridges and furrows on flexors, joints, and neck, also form cobblestone pattern on extensors surface of joints and dorsal surface of hands and feet.
  - Multiple blisters occur due to skin friction.
  - Severe hyperkeratosis leads to the shedding of scales in the superficial epidermis revealing a tender erythematous base.
  - Carpus-like scales and hyperkeratosis on the trunk, anterior neck, and flexors sometimes may outgrow into Ichthyosis Hystrix.
  - Thickened horny warty or spine-like scales on creases causing palmoplantar hyperkeratosis.
- Complications:
  - Sepsis and electrolyte imbalance (hypernatremia).
  - Foul odor (a pungent body odor), secondary infection, angular cheilitis, hair loss, hypocalcemia, vitamin D resistance, severe palmoplantar hyperkeratosis leading to severe digital contractures and deformities, and gait posture abnormalities due to excessive keratinization.
- Histopathology: (Epidermolytic Hyperkeratosis) (Diagnostic).
  - Massive orthokeratotic hyperkeratosis.
  - Hypergranulosis.
  - Lysis of keratinocytes of the granular cell layer.
- Treatment: keratolytics, topical retinoid and vitamin D preparation with the treatment of secondary bacterial infection.

Fig. 1.17 Epidermolytic ichthyosis. Hyperkeratosis with corrugated ridges and furrows on flexors (**a**). Hyperkeratosis with a cobblestone pattern on extensors surface of joints (**b**, **c**) on dorsa of feet (**d**), palmar hyperkeratosis (**e**), carpus-like scales on trunk with focal erosions (**f**, **g**)

Fig. 1.18 Epidermolytic Ichthyosis. Male patient, showing hyperkeratosis with corrugated ridges and furrows on face (**a**), flexors (**b**, **c**), extensors (**d**, **e**) with palmar hyperkeratosis (**f**)

Fig. 1.19 Epidermolytic ichthyosis. Male patient, showing hyperkeratosis with corrugated ridges and furrows on face (**a**), neck (**b**), extensors (**c**, **d**) with maceration (**e**) and palmar hyperkeratosis (**f**)

Fig. 1.20 Epidermolytic ichthyosis. Female patient showing hyperkeratosis with corrugated ridges and furrows on trunk (**a**, **b**), limbs with increasing severity on elbows and knees (**c**, **d**). Maceration is marked in hands and flexures (**e**–**i**)