Chapter 15 Disorders of Abnormal Keratinization

The mechanisms of keratinization have been clarified in recent years. The genes responsible for many hereditary disorders of abnormal keratinization have been identified, but the pathogenesis of some disorders remain unknown. It is expected that these will be elucidated in the near future.

Disorders of abnormal keratinization are classified as hereditary keratoses (e.g., ichthyosis, Darier’s disease) and acquired diseases. The acquired diseases are subclassified as inflammatory diseases, whose main symptom is inflammation accompanied by itching (e.g., psoriasis, lichen planus), and non-inflammatory keratoses (e.g., clavus, callus). This chapter discusses typical disorders of keratinization, based on that classification.

A. Hereditary keratoses

a. Ichthyosis

Ichthyosis is the clinical condition in which the whole body skin dries and becomes coarse, resulting in scaling. It is caused by abnormality in keratinization and exfoliation of the horny cell layer. The skin is covered with what appear to be fish-like scales. Patients with ichthyosis have a congenital abnormality in keratinization and scaling, and most cases are classified as hereditary keratoses. However, some may appear later in life as acquired conditions; these cases often accompany malignant tumors. Ichthyosis is classified by clinical features, inheritance pattern, and affected sites into more than ten subtypes (Table 15.1). This section introduces typical types of ichthyosis.

1. Ichthyosis vulgaris

Outline

- It is caused by mutation in the gene coding for filaggrin, a key protein involved in skin barrier function. This is the mildest form of ichthyosis. The main symptoms are dryness and scaling of the skin.
- The onset is early childhood. Dryness, and scaling of the skin are present, mostly on the extensor surfaces of extremities and trunk. It subsides during summer.
- It is the common inherited disorder of keratinization.
- Inheritance is semidominant.
- Symptomatic therapies including application of moisturizer are the main treatments.

Clinical features

The onset is early childhood. It is progressive until the patients reach about the age of 10, the symptoms subsiding in adolescence.

Table 15.1 Classification of ichthyosis.

<table>
<thead>
<tr>
<th>Congenital ichthyosis</th>
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<tbody>
<tr>
<td>Ichthyosis vulgaris</td>
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<tr>
<td>X-linked ichthyosis</td>
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<tr>
<td>Bullous congenital ichthyosiform erythroderma (BCIE)</td>
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<tr>
<td>Nonbullous congenital ichthyosiform erythroderma (NBCIE)</td>
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<tr>
<td>Lamellar ichthyosis</td>
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<tr>
<td>Harlequin ichthyosis</td>
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Ichthyosis accompanied by internal organ lesion (Ichthyosis syndrome)

<table>
<thead>
<tr>
<th>Sjögren-Larsson syndrome</th>
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<tbody>
<tr>
<td>Netherton syndrome</td>
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<tr>
<td>KID syndrome</td>
</tr>
<tr>
<td>Dorfman-Chanarin syndrome</td>
</tr>
<tr>
<td>Refsum syndrome</td>
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<tr>
<td>Rud syndrome</td>
</tr>
<tr>
<td>Rud syndrome</td>
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<tr>
<td>Conradi syndrome</td>
</tr>
</tbody>
</table>

Acquired ichthyosis

Acquired ichthyosis

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in most cases. The skin dries, appearing pityroid and lamellar. The extensor surfaces of the legs and the back region are the most commonly affected; the flexure of joints in the extremities, axillary fossae genitales and thoraco-abdominal region are unaffected (Fig. 15.1). Subjective symptoms and itching are rarely observed. The symptoms subside during the summer and aggravate during the winter, when the skin tends to dry. Filaggrin mutation is a major predisposing factor for atopic dermatitis, and atopic disorders are strongly associated with ichthyosis vulgaris.

### Pathogenesis

The causative gene has recently been identified as the filaggrin gene (FLG). As a result of a decrease in the production of filaggrin, which moisturizes the epidermis, there is abnormal exfoliation of horny cells and dryness and scaling of the skin (Chapter 1). Ichthyosis vulgaris is semidominantly inherited (homozygous patients have more severe symptoms than heterozygous patients) and often runs in families.

### Pathology

There is thickening of the horny cell layer and reduction or loss of keratohyaline granules and granular cell layer because of loss or reduction of filaggrins.

### Laboratory findings. Diagnosis

Ichthyosis vulgaris is diagnosed by the clinical and pathological features, family history and filaggrin gene mutation.

### Differential diagnosis

In other hereditary ichthyoses, the onset is the time of birth, and the flexures of the joints in the extremities are often involved (Table 15.2). Acquired ichthyosis can be differentiated from ichthyosis vulgaris by the age of onset, the clinical course, and the presence of malignant tumor in the case of the former.

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**Table 15.2 Comparison between types of ichthyosis.**

<table>
<thead>
<tr>
<th></th>
<th>Ichthyosis vulgaris</th>
<th>X-linked ichthyosis</th>
<th>Bullous congenital ichthyosiform erythroderma (BCIE)</th>
<th>Nonbullous congenital ichthyosiform erythroderma (NBCIE), lamellar ichthyosis</th>
<th>Harlequin ichthyosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Inheritance pattern</strong></td>
<td>SD (semidominant)</td>
<td>XR</td>
<td>AD</td>
<td>AR</td>
<td>AR</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>Babyhood, infancy</td>
<td>At birth or early after birth</td>
<td>At birth or early after birth</td>
<td>At birth</td>
<td>At birth</td>
</tr>
<tr>
<td><strong>Skin symptom</strong></td>
<td>Extremities, trunk (back &gt; abdomen), intertriginous sites, extensor surface &gt; flexor surface</td>
<td>Abdomen &gt; back, intertriginous sites, extensor surface = flexor surface</td>
<td>Whole body</td>
<td>Whole body</td>
<td>Whole body</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Fine scales</td>
<td>Large, dark brown scales</td>
<td>Severe hyperkeratosis</td>
<td>Flushing, fine or dark brown (NBCIE) large scales (lamellar ichthyosis)</td>
<td>Markedly thick hyperkeratosis, deep fissures, ectropion</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Hyperkeratosis, thinned granular cell layer</td>
<td>Hyperkeratosis, almost normal granular cell layer</td>
<td>Degeneration of granular cell layer</td>
<td>Hyperkeratosis (with or without parakeratosis)</td>
<td>Severe hyperkeratosis</td>
</tr>
<tr>
<td><strong>Causative gene</strong></td>
<td>Filaggrin (FLG)</td>
<td>Steroid sulfatase</td>
<td>Keratin 1 or keratin 10</td>
<td>Transglutaminase 1 in some cases</td>
<td>ABCA12</td>
</tr>
</tbody>
</table>

(AD: autosomal dominantly inherited, AR: autosomal recessively inherited, XR: x-linked recessively inherited, SD: semidominantly inherited).

**Fig. 15.1 Ichthyosis vulgaris.**
The skin dries, and pityriasis-like lamellar exfoliation occurs.
**A. Hereditary keratoses**

Treatments are symptomatic. Moisturizer, urea ointments, salicylic acid petrolatum, and vitamin D₃ ointments are applied. The symptoms subside after adolescence.

### 2. X-linked ichthyosis

**Outline**

- It is caused by loss or marked reduction of steroid sulfatase, resulting in delayed exfoliation of the horny cell layer. It is X-linked recessively inherited.
- The symptoms are severer than those of ichthyosis vulgaris. Eruptions also appear on the flexures of joints.

**Clinical features**

X-linked ichthyosis manifests shortly after birth and does not improve with age. The cutaneous symptoms are severe; the scales are large and dark brown (Fig. 15.2). The whole body of newborns may be encased in a translucent covering (collodion baby). Not only the extensor surfaces but also the flexures of extremities are affected. The abdomen is most severely affected. Corneal opacification may occur as a complication. As with ichthyosis vulgaris, X-linked ichthyosis aggravates during the winter and subsides during the summer.

**Pathogenesis**

It is caused by mutation in the steroid sulfatase gene on X-chromosome. Steroid sulfatase is the enzyme that breaks down cholesterol sulfate, a substance which promotes intercellular adhesion in the horny cell layer. The lack of steroid sulfatase causes accumulation of cholesterol sulfate, leading to delayed exfoliation of horny cells and hyperkeratosis (Chapter 1). X-linked ichthyosis is recessively inherited and occurs in males.

**Pathology, Laboratory findings**

Thickening of the horny cell layer, and normal or mildly thickened granular and suprabasal cell layers are present. Follicular keratinization is rarely found. Absence or marked reduction of steroid sulfatase is observed in the horny cell layer, peripheral leukocytes, and fibroblasts. Estriol in the urine decreases in the mothers (carriers) of children with X-linked ichthyosis.

**Differential diagnosis, Treatment**

Ichthyosis vulgaris is differentiated from X-linked ichthyosis by the decrease of steroid sulfatase in the case of the latter. The treatments are symptomatic and the same as those for ichthyosis vulgaris.

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**Fig. 15.2** X-linked ichthyosis.
Relatively large scales are present. The symptoms are severer than those of ichthyosis vulgaris.

**Fig. 15.3-1** Bullous congenital ichthyosiform erythroderma.
Skin lesions accompanied by flushing and thick keratinization occur on the whole body surface.
Patients with bullous congenital ichthyosiform erythroderma (BCIE) are sometimes born as collodion babies. Diffuse flushing and blistering recur for several weeks after birth. Scales gradually thicken, leading to severe keratinization in later childhood (Figs. 15.3-1 and 15.3-2). The thickly keratinized plaques are accompanied by flush and a characteristic odor. The whole body including the flexures of joints and extremities appear erythrodermatic and dark rose in color. The prognosis is good.

**Clinical features**

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**Pathogenesis**

The cytoskeleton (intermediate filament) of suprabasal cells is
composed of keratin 1 and keratin 10. Because of mutation in the keratin 1 or keratin 10 gene, abnormal keratin fiber formation, cytoskeleton distortion, and epidermal blistering occur, leading to secondary thickening of the horny cell layer (Fig. 1.14). BCIE is autosomal dominantly inherited.

**Pathology**

The horny and suprabasal cell layers thicken, keratin fibers aggregate, and there are vacuolated cells containing large keratohyaline granules in the granular and suprabasal cell layers (granular degeneration, Fig. 15.4).

**Differential diagnosis, Treatment**

Blistering is marked, particularly in newborns. It is necessary to differentiate BCIE from epidermolysis bullosa, incontinentia pigmenti and impetigo contagiosa by the pathological findings. The treatments are oral retinoid and application of moisturizer.

**4. Ichthyosis bullosa of Siemens**

It is caused by mutation in the keratin 2e gene. The clinical features are similar to those of the mild type of bullous congenital ichthyosiform erythroderma; nonetheless, erythroderma is not present in ichthyosis bullosa of Siemens (Fig. 15.5). Localized granular degeneration is histopathologically seen in part of the uppermost prickle layer and granular layer where keratin 2e is expressed in the epidermal granular layer.

**5. Nonbullous congenital ichthyosiform erythroderma (NBCIE)**

**Clinical features**

Most of the patients are born as collodion babies. Two to three days after birth, the collodion covering exfoliates, leaving the whole body surface with diffuse flushing and scaling (Figs. 15.6-1 and 15.6-2). The affected sites include the flexures of joints. Ectropion of eyelids may also occur. There are minor changes in the symptoms with season. NBCIE progresses until the age of 10, at which point it stops and subsides. The clinical manifestations range from mild to severe.

**Pathogenesis**

It is autosomal recessively inherited. The pathogeneses are various. Six or more genes are thought to be associated with occurrence of NBCIE. A certain mutation in the ABCA12 gene, the causative gene for harlequin ichthyosis, also causes NBCIE. The transglutaminase 1 gene, the causative gene for lamellar ichthyosis, can also cause NBCIE. Complete absence of transglutaminase 1 activity causes typical lamellar ichthyosis; severe reduction in such activity leads to NBCIE. The mechanism of
Cornified cell envelopes cover the horny cell membrane in the horny cell layer. They play an important role in increasing the strength of the horny cell layer against physical and chemical stimuli.

Fig. 15.6-2 Nonbullous congenital ichthyosiform erythroderma.

Fig. 15.7 Cornified cell envelope.
NBCIE is known to be a marked decrease in physical and functional strength of keratin (Figs. 15.7 and 1.16).

**Treatment**

Oral retinoid (a vitamin A derivative) is effective. The skin should be kept clean to prevent secondary infection.

### 6. Lamellar ichthyosis

In approximately half of all cases of lamellar ichthyosis, the cause is an absence of transglutaminase 1; however, its activity is normal in some cases. Transglutaminase 1 is a calcium-dependent enzyme that is necessary for the formation of cornified cell envelopes in keratinocytes. The pathogenesis of lamellar ichthyosis are various. The scales in lamellar ichthyosis are clinically rough and large in most cases, dark brown, and plate-like or lamellar; these characteristics distinguish the scales from those in nonbullous congenital ichthyosiform erythroderma (NBCIE) (Fig. 15.8).

### 7. Harlequin ichthyosis

**Synonym:** Harlequin fetus

The patient is covered with an extremely thick stratum corneum at birth. Cracks in the skin, ectropion of eyelids, protrusion of lips, and difficulty of opening the mouth are so severe that most patients die within 2 weeks after birth (Fig. 15.9). In 2005, a Japanese dermatologist identified ABCA12 as the causative gene. ABCA12 is a lipid transporter in the lamellar granule, and the lack of ABCA12 leads to marked reduction of lipid content in the horny layer. There is abnormality of the lamellar granules in harlequin ichthyosis. It is autosomal recessively inherited, and DNA-based prenatal diagnosis is clinically applied.

### 8. Ichthyosis syndrome

Ichthyosis syndrome is a general term for congenital ichthyosis accompanied by involvement of certain organs. Most of the cutaneous symptoms resemble those of nonbullous congenital ichthyosiform erythroderma (NBCIE). The most frequently occurring types of ichthyosis syndrome are listed in Table 15.3.

1. **Sjögren-Larsson syndrome**

   It is autosomal recessively inherited. The main characteristics are congenital ichthyosiform erythroderma, spasmodyc acroparesthesia, and mild to moderate mental retardation (Fig. 15.12). There is abnormality in the gene that codes for fatty aldehyde dehydrogenase (FALDH/ALD). The condition is caused by absence of FALDH.

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**Fig. 15.8 Lamellar ichthyosis.**

Large, dark brown scales are characteristic of lamellar ichthyosis.

**Fig. 15.9 Harlequin ichthyosis.**

There is marked hyperkeratosis on the whole body surface. Ectropion of the eyelids results in reddening over the eyes. Normal eyeballs are present underneath.
15 Disorders of Abnormal Keratinization

Table 15.3 Major ichthyosis syndromes.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance pattern</th>
<th>Eruptions</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren-Larsson syndrome</td>
<td>AR</td>
<td>Nonbullous congenital ichthyosiform erythroderma</td>
<td>Mental retardation, spastic quadriplegia</td>
</tr>
<tr>
<td>Netherton syndrome</td>
<td>AR</td>
<td>Atopic dermatitis-like eruption, bamboo hair</td>
<td>Atopic diathesis</td>
</tr>
<tr>
<td>KID syndrome</td>
<td>AD</td>
<td>Spiny hyperkeratosis in the extremities and face</td>
<td>Hearing impairment, keratitis</td>
</tr>
<tr>
<td>Dorfman-Chanarin syndrome</td>
<td>AR</td>
<td>Nonbullous congenital ichthyosiform erythroderma</td>
<td>Lipid droplets in leukocytes, hepatic steatosis, cataract, neurologic manifestation</td>
</tr>
<tr>
<td>Refsum syndrome</td>
<td>AR</td>
<td>Lamellar ichthyosis-like skin</td>
<td>Retinitis pigmentosa, polyneuropathy, cerebellar ataxia, inner-ear deafness</td>
</tr>
<tr>
<td>Rud syndrome</td>
<td>AR</td>
<td>Nonbullous congenital ichthyosiform erythroderma</td>
<td>Seizure, mental retardation, low height, gonadal hypofunction</td>
</tr>
<tr>
<td>Conradi syndrome</td>
<td>AD or AR</td>
<td>Nonbullous congenital ichthyosiform erythroderma</td>
<td>Skeletal defects, cataract, punctate shadow at bone ends, quadriplegia</td>
</tr>
</tbody>
</table>

(AR: autosomal recessively inherited, AD: autosomal dominantly inherited).

Clinical images are available in hardcopy only.

Fig. 15.12 Sjögren-Larsson syndrome.
Nonbullous congenital ichthyosiform erythroderma-like eruptions occur.

2 Netherton syndrome
Autosomal recessively inherited, it is caused by a mutation in the SPINK5 gene, which codes for serine protease inhibitor. The eruptions resemble atopic dermatitis or nonbullous congenital ichthyosiform erythroderma (Fig. 15.10). Scalp hair becomes knotted, short and easily broken (bamboo hair).

KID syndrome
It is autosomal dominantly inherited. The main symptoms are keratitis, ichthyosis and deafness. Papillomatous or prickle keratotic lesions occur mainly on the face and extremities (Fig. 15.11).

4 Dorfman-Chanarin syndrome
It is an autosomal recessively inherited metabolic disorder of neutral lipids, caused by mutation in the CGI-58 gene, which codes for an enzyme that regulates metabolism of phospholipids. Triacylglycerol accumulates in the cytoplasm of various cells to form lipid droplets. The disorder may be accompanied by ichthyosis, liver disorder, hearing loss, mental retardation, cataract and nystagmus (Figs. 15.13 and 15.14).

5 Refsum syndrome
It is autosomal recessively inherited. In addition to lamellar-ichthyosis-like eruptions, there is night blindness caused by
retinitis pigmentosa. Cerebellar ataxia, multiple neuritis polyneuritis, and sensorineural deafness are present. Levels of phytanic acid in the blood increase from congenital metabolic disorder.

Rud syndrome
It is known to be autosomal recessively inherited; boys are more commonly affected than girls, and most cases are sporadic. Congenital ichthyosiform erythroderma-like skin manifestations, epilepsy, mental retardation, gonadal hypofunction and short stature may occur as complications.

Conradi syndrome (Conradi-Hünermann-Happle syndrome)
The symptoms of nonbullous congenital ichthyosiform erythroderma, abnormal formation of bones, cataract, and paralysis in all extremities occur. Conradi syndrome is X-linked dominantly inherited. Males die prenatally. The cause is mutation in the emopamil binding protein (EBP) gene at Xp11.22-p11.23.

b. Palmoplantar keratoderma

Definition, Classification
Palmoplantar keratoderma is a generic term for diseases that hereditarily cause hyperkeratosis in the palms and soles. It is sub-classified by clinical features and patterns of inheritance (Figs. 15.15-1 and 15.15-2; Table 15.4). Genetic mutation is identified in some cases. Further clarification is necessary for exact classification of palmoplantar keratoderma. The main types of palmoplantar keratoderma are shown below.

Treatment
There is no effective treatment for any types. Oral retinoid (a vitamin A derivative) and topical application of petrolatum salicylate or moisturizer are the main treatments.