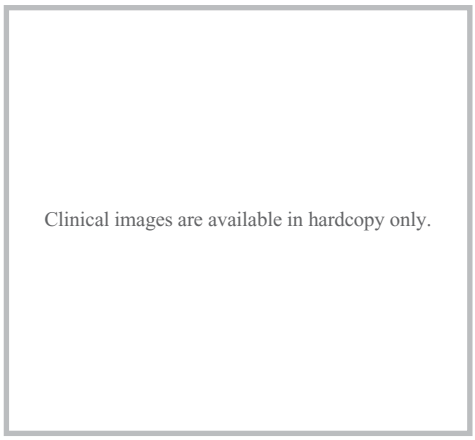

Fig. 20.26 Nevus anemicus.

4. Nevus anemicus ★

A sharply circumscribed white patch occurs, often on the upper chest, when the skin is flushed by bathing or rubbing. Known to be capillary dysfunction (catecholamine sensitivity), it may accompany neurofibromatosis type 1 (NF1) or nodular sclerosis.

Neurocutaneous syndrome

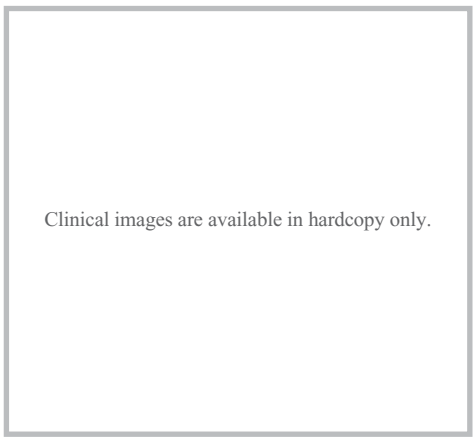

Fig. 20.27-1 Café-au-lait spot caused by neurofibromatosis type 1 (NF1).

1. Neurofibromatosis type 1 (NF1) ★★

Synonym: Von Recklinghausen disease

Outline

- It is a neurocutaneous syndrome caused by proliferation of cells that originate from neural crests. Neurofibroma, pigmentation and nervous tumor in multiple organs are the main symptoms.
- It is autosomal dominantly inherited, characterized by multiple pigmentation (café-au-lait spots) at birth and soft tumors (neurofibromas) after infancy.
- Surgical removal and laser therapy are conducted.

Clinical features

① Café-au-lait spot

This is a flat, oval eruption of the color of coffee with cream or darker brown. It varies in size and appears on the trunk and extremities. A café-au-lait spot with a diameter of about 10 cm is called a large Recklinghausen spot; one with a diameter of 1 cm or less is called a small Recklinghausen spot. Individual eruptions cannot be distinguished from nevus spilus. A café-au-lait spot on the axillary fossae, called axillary freckling, is thought to be a specific symptom of NF1. The pigmentation of the spot is solid (**Figs. 20.27-1** and **20.27-2**). Café-au-lait spots are present in 70% of all newborns. After infancy, the number of spots does not increase.

② Neurofibroma

A neurofibroma is a soft tumor of normal skin color or light brownish-pink of various sizes (**Figs. 20.28-1** and **20.28-2**). It may be produced on any site of skin. It may be elevated and dome-shaped or papillary, or flat and palpable. Valvular or hanging

neurofibroma is called diffuse plexiform neurofibroma or pachydermatocele (**Fig. 20.29**). Neurofibroma first appears between childhood and puberty, after which it gradually enlarges and increases in number. It may increase rapidly during pregnancy and after delivery.

Nodular plexiform neurofibroma, neurofibroma in the peripheral nerves, is a slightly palpable, spindle-shaped tumor that appears on the skin over the subcutaneous nerves. It may appear in a beaded linear pattern and be accompanied by tenderness or radiating pain.

③ Other skin lesions caused by NF1

Nevus anemicus may occur in some cases with NF1. Small yellow tumors may appear on the face and scalp of infants and disappear spontaneously in several years (juvenile xanthoendothelioma).

④ Other symptoms of NF1

Central nervous symptoms include neurofibroma in the brain and spiral nerves, gliacytic tumor, meningioma, convulsive seizure, and mental retardation or learning impairment. Bone abnormality, including scoliosis, deformity or bone defect in the thorax, occurs in about half of all cases. Ocular symptoms of NF1 are irridic nodules, called Lisch nodules, and orbital neurofibroma in which ophthalmocele may occur. Congenital glaucoma and retinal tumor may occur.

Classification

Neurofibromatosis (NF) is pathologically classified into 8 types: NF1 through NF8. NF1 is the most common and occurs in 1 in 3,000 births. It is autosomal dominantly inherited, and 60% to 70% of NF1 cases are sporadic and caused by genetic mutation. Occurrence of NF3 through NF8 is extremely rare.

Pathogenesis

The gene involved in NF1 is on chromosome 17 (17q11.2). It produces neurofibromin, a tumor suppressor. In NF1, gene mutation in 17q11.2 is thought to increase proliferation of cells (the penetration rate of NF1 is 100%).

Pathology

Neurofibroma is formed by Schwann cells and intraneural fibroblasts, with thin undulating collagen fibers in the middle (**Fig. 20.30**). Schwann cells test positive for S-100 protein antibodies.

Diagnosis

NF1 is easily diagnosed by café-au-lait spots and neurofibroma. Although NF1 in childhood is difficult to diagnose because a few café-au-lait spots are the only symptom, the likelihood of NF1 is high when there are six or more café-au-lait spots (the 6-spot criterion) or when there is a Recklinghausen patch on the axillary fossae. The criteria for NF1 established by the National

Clinical images are available in hardcopy only.

Fig. 20.27-2 Café-au-lait spot caused by NF 1.
Many small café-au-lait spots are present on the axilla.

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Fig. 20.28-1 Neurofibroma caused by NF 1.

Fig. 20.28-2 Neurofibromatosis type 1 (NF1).

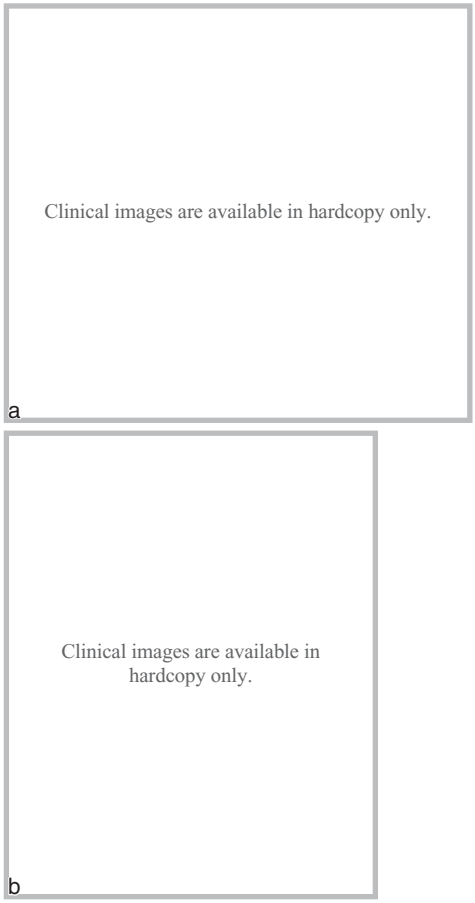


Fig. 20.29 Diffuse plexiform neurofibroma, pachydermatocele.
a: Affected breast. b: Side of the body. The lesion has been partially removed by excision and suturing.

Institutes of Health are shown in **Table 20.2**. Even areas that are not sun-exposed may be involved in NF1, which distinguishes the condition from freckles.

Treatment

Symptomatic therapy is the main treatment. Café-au-lait spots are treated by laser therapy and dermabrasion; nevertheless, they tend to recur. Neurofibromas on highly visible areas such as the face or extremities are surgically removed. When a diffuse plexiform neurofibroma is excised, there is a risk of massive perioperative hemorrhage.

Prognosis

As NF1 is a progressive disease, numerous neurofibromas may occur on the whole body after middle age. The prognosis tends to be good. The central nervous lesion and neurofibroma may worsen and develop a malignant peripheral nerve sheath tumor in rare cases.

2. Neurofibromatosis type 2 (NF2)

Clinical features

An elastic, firm, sharply margined subcutaneous neurilemmoma is the main cutaneous symptom. The café-au-lait spots seen with NF1 are not observed. Lesions in the central nervous system, such as acoustic schwannoma (vestibular sheath tumor), are the main symptoms of neurofibromatosis type 2 (NF2). Hearing impairment and dizziness are present. Paralysis in the extremities and reduced sensory perception are induced by enlargement of the tumor.

Pathogenesis, Epidemiology

NF2 is autosomal dominantly inherited. It occurs in 1 in 50,000 to 1 in 100,000 persons. About half of the cases are sporadic. The related gene on chromosome 22 (22q12) codes for a protein called merlin (a moesin-ezrin-radxin-like protein), whose structure is similar to that of cytoskeleton proteins. NF2 is caused by mutation of this gene; however, the mechanism is unknown.

Pathology

Verocay bodies, which are characteristic to neurilemmoma, are found in NF2. Neurofibromas, which develop in NF1, are not found in NF2.

Treatment, Prognosis

Total resection of the neurotumor is the basic treatment. Removal may impair hearing. Because tumors enlarge unexpectedly, it is difficult to determine the policy of treatment considering the prognosis for cases with NF2. NF2 has a worse prognosis than NF1.

3. Tuberous sclerosis ★★

Synonym: Bourneville-Pringle's phacomatosis

Outline

- The main symptoms are multiple facial angiofibroma, intelligence impairment and convulsive seizure.
- It is autosomal dominantly inherited.
- It is characterized by white leaf-shaped macules in infancy and multiple papules (angiofibroma) that occur around the nose after early childhood. Shagreen patch and Koenen's tumor are also important findings.

Clinical features

① Facial angiofibroma

Multiple firm papules of normal skin color or light pink and 2 mm to 10 mm in diameter appear symmetrically on the nasolabial sulcus, cheeks, and the area around the nose (**Fig. 20.31**). The papules occur in about 90% of cases with tuberous sclerosis; the papules and their high specificity are useful for diagnosis of facial angioma. Facial angiofibromas do not appear until the ages of 3 to 4 in most cases, and they become more numerous with age. As the patient grows, the eruptions coalesce to take on a tumorous or plaque-like appearance. Facial angiofibroma used to be called adenoma sebaceum but now is called angiofibroma, because the main pathological condition is degeneration of the blood vessels and connective tissue.

② Shagreen patch

Shagreen patch is a special subtype of connective tissue nevus. Shagreen refers to rough, untanned leather. Firm, flatly elevated lesions of about 3 cm in diameter occur mainly on the lumbar

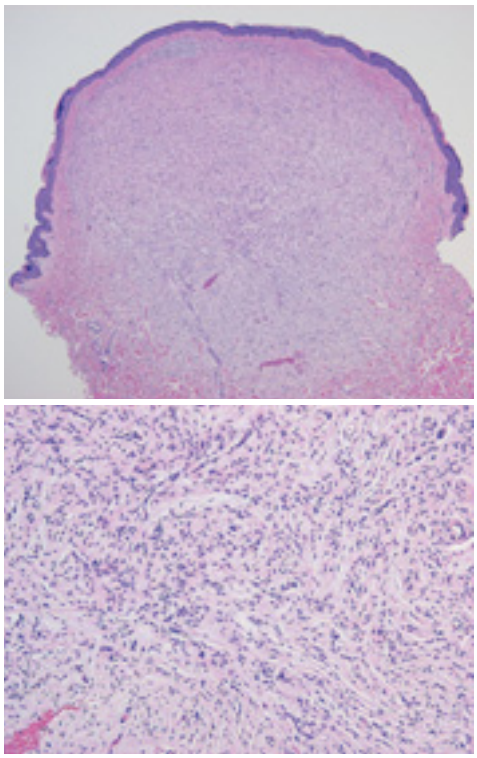
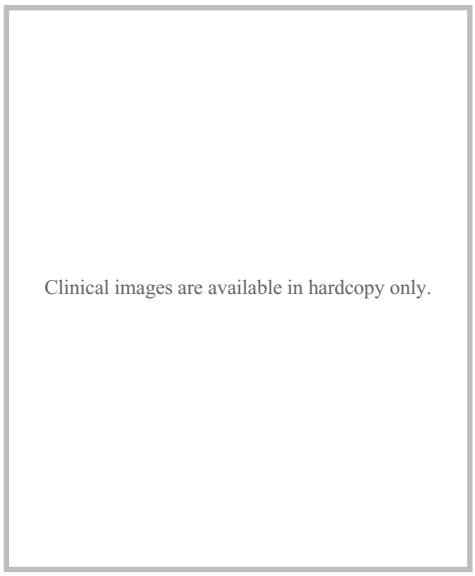


Fig. 20.30 Histopathology of neurofibroma.

Table 20.2 Diagnostic criteria of neurofibromatosis type 1 and type 2 (NIH).

Neurofibromatosis-1 (NF1)
At least 2 of the following 1. Six or more café-au-lait spots of 5 mm or more in diameter (before adolescence) Six or more café-au-lait spots of 15 mm or more in diameter (after adolescence) 2. Two or more neurofibroma, or at least 1 neurofibroma in the peripheral nerves 3. Pigmented macules in the axillary fossae or the groin 4. Neurofibroma in the eye socket 5. Two or more Lisch nodules 6. Bone abnormality 7. Family history of NF1
Neurofibromatosis-2 (NF2)
At least 1 of the following 1. Tumors in the acoustic nerves on the both sides observed by CT or MRI 2. Family history of NF2 and the patient has a unilateral acoustic tumor, or at least 2 of the following: neurofibroma, meningioma, glioma, neurilemmoma, juvenile cataract



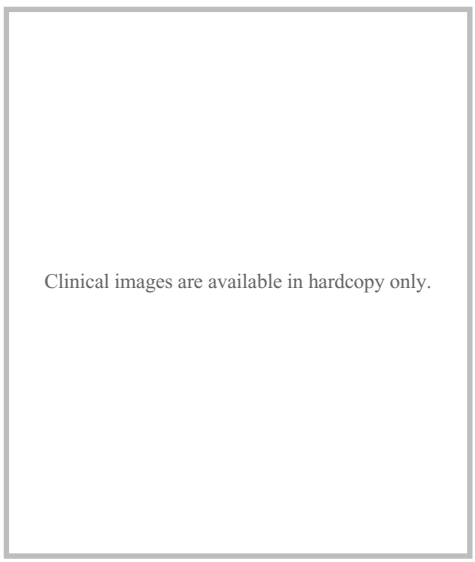


Fig. 20.31 Tuberous sclerosis.
Angiofibroma on the face.

Fig. 20.32 Koenen's tumor.

region and buttocks and coalesce in an arabesque pattern. They often become marked after puberty. Shagreen patch is thought to be a connective-tissue nevus of the sacral region.

③ White leaf-shaped macules

White leaf-shaped macules are oblong depigmentations caused by reduced production of melanin, most frequently on the trunk and lower legs. They are seen in about half of all cases with tuberous sclerosis. The onset is usually infancy, and prompt discovery is important. However, they may occur in adults in rare cases. Careful inspection is required for diagnosis. Wood's lamp is helpful for observation. The white leaf-shaped macules do not become more numerous over time.

④ Koenen's tumor

Angiofibroma appears on the edge or surface of the nail plate (**Fig. 20.32**). Small spindle-shaped nodules with a diameter of 2 mm to 10 mm and a color range of light pink to brown appear. The nodules are as firm as cartilage.

⑤ Central nervous symptoms

Convulsive seizure and intelligence impairment are the main symptoms. Convulsive seizure occurs in about half of all patients with tuberous sclerosis; it subsides within one year after birth. Various symptoms including epilepsia nutans, Lennox-Gastaut syndrome, and tonic-clonic epilepsy are present. Mental retardation may also occur.

⑥ Other symptoms of tuberous fibroma

Translucent tumor (astrocytic hamartoma) in the retina and lamellar leukoderma in the iris may occur. Honeycomb lung may be caused in rare cases. Rhabdomyoma may occur in the heart as a complication. Many cases are asymptomatic. Angiomyolipoma and renal failure from hydronephrosis and renal cyst often occur.

Pathogenesis

The genes responsible for tuberous sclerosis are TSC1 (tuberous sclerosis complex 1) on chromosome 9 (9q34) and TSC2 on chromosome 16 (16p13.3). Both are thought to play a role in tumor suppression. Although tuberous sclerosis is autosomal dominantly inherited, 60% to 70% of all cases are sporadic and there are relatively few familial cases.

Laboratory findings

Nodule-like calcium deposition on the lateral ventricular walls and basal nuclei and enlargement of the lateral ventricle are found by head CT scan. A nodule-like tumor is observed by MRI in the cerebral cortex. The pathology is that of an anastrocytic hamartoma.

Diagnosis

Tuberous sclerosis is easily diagnosed by the cutaneous symptoms, which include multiple angiofibroma of the face. Calcium deposition and nodules observed by CT scan and MRI are diagnostic, as is ocular fundus tumor. Electroencephalogram and

renal angiography are also helpful for diagnosis.

Treatment, Prognosis

Dermabrasion, excision, cryotherapy and laser therapy are conducted on the cutaneous lesions for cosmetic reasons, which nevertheless tend to recur. Drug therapy is useful for convulsive seizure. There is no treatment for the progressive mental retardation. The prognosis depends on the severity of cerebral tumorous lesions and renal leisions.

4. Peutz-Jeghers syndrome ★★

Outline

- Autosomal dominantly inherited, it is characterized by pigmentation on the lips, oral mucosa and distal extremities, and gastrointestinal polyposis.
- Careful observation is required, because intussusception and cancer may develop as a result of gastrointestinal polyps.
- Laser therapy, dermabrasion and polypectomy are conducted.

Clinical features

① Skin pigmentation

Flat, asymptomatic, sharply margined, blackish-brown macules of 2 mm to 10 mm in diameter occur symmetrically on the lips, oral mucosa, palms and soles (distal extremities in particular) (**Fig. 20.33**). The longitudinal axis of the macule runs parallel to the dermatoglyphic lines. Pigmentation is darkest in the crista cutis and lightest in the sulcus cutis. Pigmentation appears between the time of birth and infancy, and tends to increase in number and size with age; it fades in adulthood.

② Gastrointestinal polyposis

Gastrointestinal polyposis may occur in any part of the gastrointestinal tract, especially the jejunum. A single lesion or more than ten may be produced. They tend to cause intussusception leading to intense abdominal pain and melena. Most cases of gastrointestinal polyposis are histologically hamartoma; the tissue structure of the lesion is normal and malignant transformation rarely occurs (**Table 20.3**). Adenoma occurs in about 10% of cases and may become cancerous.

Pathogenesis

Peutz-Jeghers syndrome is autosomal dominantly inherited; however, about half of all cases occur sporadically. It is caused by mutation in the LKB1 gene on chromosome 19 (19p13.3). The LKB1 gene codes for a serine-threonine kinase whose activity is lost in many patients with Peutz-Jeghers syndrome. The mechanism is unknown.

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Fig. 20.33 Peutz-Jeghers syndrome.
Pigmentation occurred on the lips and hand.

Table 20.3 Major cutaneous symptoms accompanying gastrointestinal polyposis.

Disease	Inheritance pattern	Sites where polyps likely form	Canceration of polyp?	Cutaneous symptoms
Peutz-Jeghers syndrome	Autosomal dominant	Jejunum in many cases	Sometimes	Pigmented macules on the lips, oral mucosa and palms
Cronkhite-Canada syndrome	Not inherited	Entire digestive tract	No	Alopecia, nail plate abnormality, pigmented macules on the dorsum of hands
Gardner syndrome	Autosomal dominant	Large intestine in most cases	Yes	Neurofibromatosis, lipoma, dental dysplasia
Turcot syndrome	Autosomal recessive	Large intestine	Sometimes	Nervous system tumors

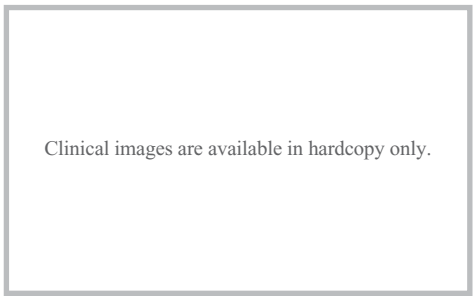


Fig. 20.34 Incontinentia pigmenti.

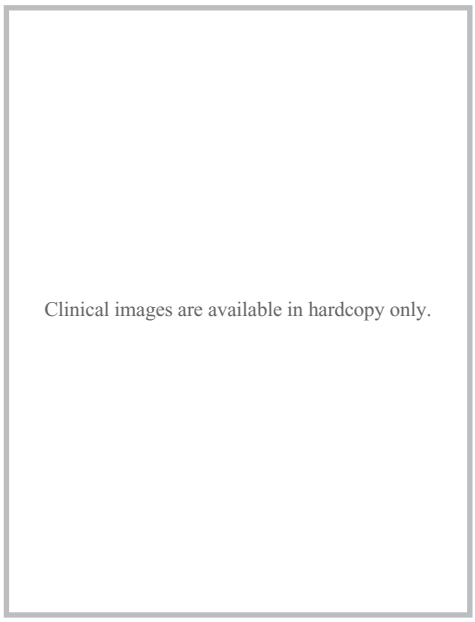


Fig. 20.35-1 Incontinentia pigmenti at the inflammatory stage.

Pathology

Melanocytes and melanin pigment increase in the epidermal basal layer. There is hyperpigmentation in the crista profunda intermedia, which is the thick portion of the epidermis. The cutaneous lesions do not show malignancy.

Differential diagnosis

As with Peutz-Jeghers syndrome, Cronkhite-Canada syndrome is characterized by gastrointestinal polyposis and pigmentation (especially on the dorsal hands). However, the onset of Cronkhite-Canada syndrome is at middle age or later and the condition is not inherited. Alopecia and abnormality of nail plate also occur in Cronkhite-Canada syndrome.

Treatment, Prognosis

Alexandrite laser therapy and dermabrasion are effective in reducing pigmentation when there are cosmetic concerns. Endoscopic or surgical excision is conducted on gastrointestinal polyps.

5. Incontinentia pigmenti (Fig. 20.34) ★★

Synonym: Bloch-Sulzberger syndrome

Outline

- Characteristic pigmentation occurs on the skin. The symptoms are clinically classified into 4 stages.
- Blistering and erythema occur at birth. The disease course begins with papules that progress to pigmentation and disappear.
- It is X-chromosome dominantly inherited; female patients greatly outnumber male patients.
- The prognosis is good. Ocular symptoms and deformity are treated.

Clinical features

Incontinentia pigmenti is classified by the clinical features.

① **Cutaneous symptoms**

Inflammatory stage: Vesicles accompanied by erythema appear, most commonly on the trunk (**Figs. 21.35-1** and **21.35-2**). The

onset is within a week after birth. They become pustules or erosion, persisting for several weeks to several months before healing gradually. Eruptions resembling alopecia plaques may occur on the scalp.

Verrucous and lichenoid stage: After the blisters subside (6 to 12 weeks after birth), multiple hyperkeratotic verrucous papules occur, mainly on the distal extremities. Most cases resolve in several months, but some persist until adulthood (**Fig. 20.36**).

Pigmented stage: Grayish-brown or purplish-brown pigmentation becomes distinct around 6 months after birth at sites where eruptions were. The pigmentation often appears in linear, droplet-like, marbled and reticular patterns (**Fig. 20.37**).

Regression stage: Pigmentation begins to disappear at age 4 or 5. It disappears completely at puberty in most cases.

② Symptoms of incontinentia pigmenti in sites other than skin

Ocular symptoms: Ocular symptoms develop in about one third of incontinentia pigmenti cases. Strabismus is the most common such symptom, followed in frequency by cataract, glioma and microphthalmos. There are findings similar to those of retinopathy of prematurity.

Central symptoms: Epilepsy and intelligence impairment may be caused in rare cases. Abnormality may occur in teeth (e.g., deficiency, developmental retardation, odontoparallaxis) and bones (e.g., dwarfism, hyperdactylia).

Pathogenesis, Epidemiology

Incontinentia pigmenti is caused by mutation in NEMO (NF-κB essential modulator), which is mapped on Xq28. It is an X-linked dominant trait that is usually lethal in males; most male fetuses with the genetic abnormality are not carried to term, which is why more than 95% of all patients are females. More than 700 cases have been reported. About half of all cases occur sporadically.

Pathology, Laboratory findings

There is eosinophilic infiltration in the intraepidermal blisters of the first stage (**Fig. 20.31**). Eosinophil levels in the peripheral blood are elevated in 30% of cases. Verrucous papules of the second stage are structurally similar to epidermal nevus. Melanophages are observed in large numbers in the upper dermal layer of pigmentation at the third stage. In the fourth stage, melanophages in the upper layer decrease.

Diagnosis, Differential diagnosis

It is easy to diagnose incontinentia pigmenti by the characteristic clinical features. The condition is sometimes misdiagnosed as epidermolysis bullosa because of blistering at birth; however, incontinentia pigmenti can be distinguished by its eosinophilic infiltration. Ocular examination is essential, because blindness and amblyopia may occur.

Clinical images are available in hardcopy only.

Clinical images are available in hardcopy only.

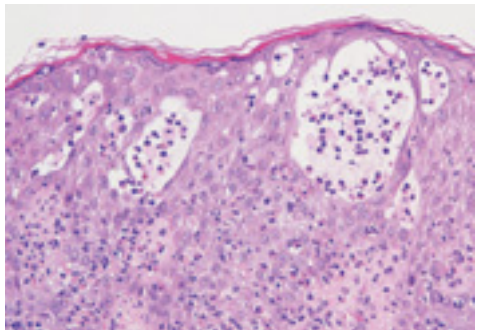


Fig. 20.35-2 Incontinentia pigmenti at the inflammatory stage.
bottom: Eosinophilic infiltration in the epidermis is characteristically seen.

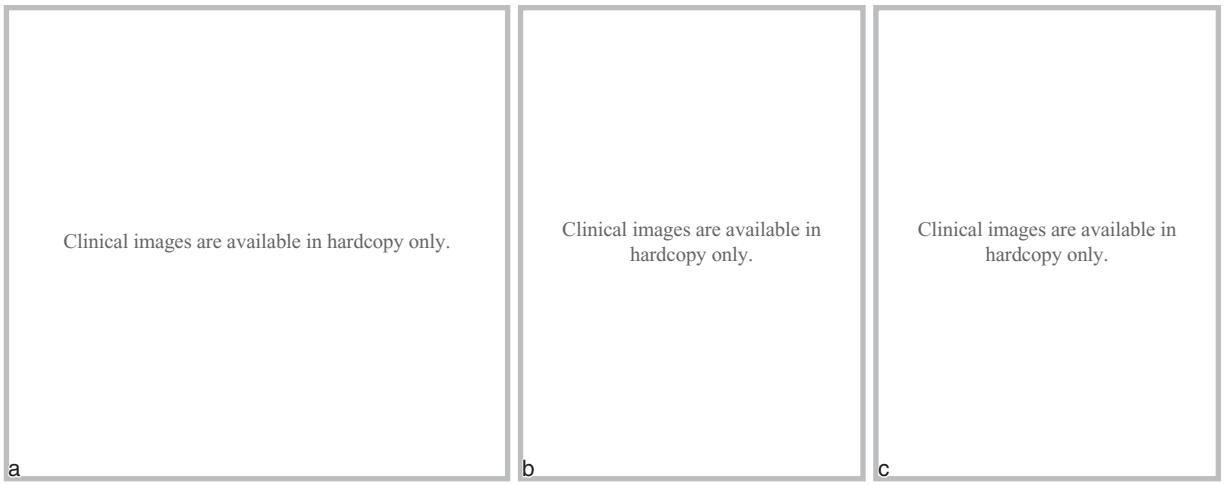


Fig. 20.36 Incontinentia pigmenti at the verrucous and lichenoid stage.
a: Eruptions on the scalp. Alopecia also occurred. b: Reticular pigmentation. c: Verrucous eruptions accompanied by severe hyperkeratosis, which resembles epidermal nevus.

Fig. 20.37 Incontinentia pigmenti at the pigmented stage.
Pigmentation appears in various degrees.

Treatment, Prognosis

Complications associated with incontinentia pigmenti and deformities should be promptly treated. As the skin lesion heals spontaneously in many cases, symptomatic therapy may be performed if necessary. The prognosis is good. About half of all male fetuses whose mothers have incontinentia pigmenti do not survive to term. Half of all girls whose mothers have incontinentia pigmenti also have the disease.

6. Sturge-Weber syndrome ★★

Outline

- Hemifacial hemangioma simplex, choroidal hemangioma and hemangioma of the leptomeninx are the main symptoms.
- The disease is nonhereditary.
- The distribution of facial hemangioma is unilateral on the area over the first division of the trigeminal nerve.
- Glaucoma is caused by hemangioma, leading to buphthalmia.
- Laser therapy, resection of the brain and ocular treatments are conducted.

Clinical features

Sturge-Weber syndrome is characterized by hemifacial hemangioma simplex, choroidal hemangioma, and hemangioma of the leptomeninx; however, most cases are incomplete, with only hemifacial hemangioma simplex and hemangioma of the leptomeninx.

Cutaneous symptoms: Unilateral, or bilateral in rare cases, flat hemangioma simplex is present at birth on the skin over the first or second division of the trigeminal nerve of the face (**Fig. 20.38**).

Central nervous symptoms: Hemangioma of the leptomeninx occurs on the side with semi-facial angioma, especially on the occipital lobe. Contralateral hemiplegia may occur in some cases. Convulsive seizure appears in infancy in about 80% of cases. Atrophy and calcinosis of the cerebral hemisphere and intelligence impairment may also occur.

Ocular symptoms: Choroidal angioma may occur on the side with semi-facial angioma, leading to abnormal formation of the anterior chamber of eyes. High fluid pressure is present in the eyes (glaucoma) in early childhood as a result. The cornea is hyperextended by increased fluid pressure of the eyes, and the corneal diameter enlarges accordingly, a condition called buphthalmia. The result is blindness in most cases.

Pathogenesis

Abnormal development of blood vessels caused by embryonic impairment of the sympathetic nerve is thought to cause Sturge-Weber syndrome; however, the details are unknown. It is congenital; nevertheless, it is known to be nonhereditary in general. It occurs in about 1 in 100,000 people.

Laboratory findings

The double-contoured calcification observed along the cerebral convolution by skull X-ray is called tramline calcification. Head CT scan and MRI are able to find angioma before calcification occurs; this is useful for early diagnosis.

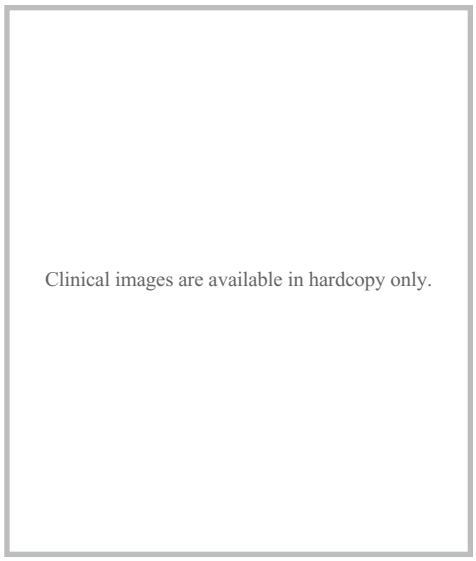


Fig. 20.38 Sturge-Weber syndrome.

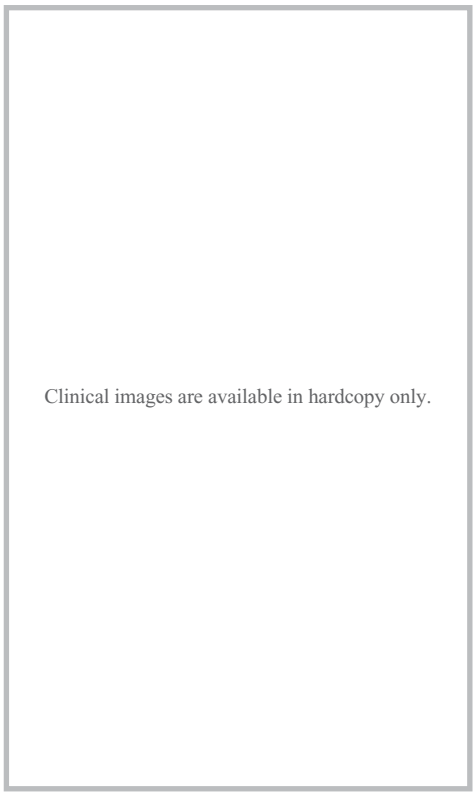


Fig. 20.39 Klippel-Trenaunay-Weber syndrome.
The right arm, which is affected by hemangioma, is longer than the left arm.

Treatment

Laser therapy is performed on facial hemangioma. When drug therapy is ineffective on convulsive seizure, resection of the brain hemangioma is conducted. For ocular symptoms, early diagnosis and adjustment of ocular pressure are important.

7. Klippel-Trenaunay-Weber syndrome ★

Synonyms: Klippel-Trenaunay syndrome, Klippel-Weber syndrome

Outline

- Hemangioma simplex in the extremities and enlargement and extension of the affected limb are observed.
- Spinal curvature is caused by the different length of the extremities, and there is the risk of ulceration and heart failure caused by arteriovenous fistula.
- Symptomatic therapy is the main treatment.

Clinical features, Pathogenesis

The cause of Klippel-Trenaunay-Weber syndrome is unknown; however, there is fragility of mesodermal tissue in the vascular walls. Cutaneous hemangioma simplex is present at birth in many cases. Usually one arm or leg, but sometimes both arms or legs, is involved. It may spread beyond the extremities (**Fig. 20.39**). Lymphangioma, congenital venectasia, angiokeratoma and congenital arteriovenous fistula may also occur and become distinct with age. These vascular lesions may cause edema, ulceration and varix secondarily. Klippel-Trenaunay-Weber syndrome is also characterized by enlargement and overgrowth of the bone and soft tissue: The extremities may become different in length and the difference becomes more distinct with age. The bone abnormality usually occurs in the leg on the same side of the body as the skin lesion, or rarely, on the opposing side. The different length of the legs results in claudication and compensatory scoliosis. Angioma in internal organs, syndactylism or other dysplasia of fingers and toes, and heart failure (if the arteriovenous fistula is severe) may occur. Abnormality of coagulation may be caused in vascular channels. Severe clotting abnormality called Kasabach-Merritt syndrome may occur in some cases.

Diagnosis, Treatment

Klippel-Trenaunay-Weber syndrome is easily diagnosed by the characteristic clinical features. Diagnosis can be confirmed by bone radiography and systemic CT scan. Arteriovenous fistula is examined by thermography, blood gas analysis and angiography. Symptomatic therapy is the main treatment. Laser therapy is conducted when the hemangioma simplex raises cosmetic concerns. Ligation or excision is performed on arteriovenous fistulae, because they may cause heart failure. For prevention of

arthropathy and curvature caused by the different length of the extremities, orthopedic shoes and osteotomy are helpful.

8. Neurocutaneous melanosis ★

Synonym: Mélanoses neurocutanées

Clinical features

Neurocutaneous melanosis is nonfamilial and occurs in both men and women. Large congenital melanocytic nevus, in most cases a giant hairy pigmented nevus, is present on nearly half the trunk (**Figs. 20.40-1** and **20.40-2**) or multiple congenital small melanocytic nevi disperse over the whole body. These nevi can be a serious burden cosmetically.

Cerebral nervous symptoms such as increased intracranial pressure and secondary hydrocephalia occur. These are accompanied by headache, vomiting, epileptic seizure and intelligence impairment. Malignant melanoma often develops on the site of the body with giant hairy nevus and leptomeninx.

Pathogenesis

Neurocutaneous melanosis is caused by proliferation of melanoblasts that originate from neural crests in the skin and central nervous system (e.g., leptomeninx). Congenital, extensive or disseminated melanocytic nevi occur. In the brain, perivascular proliferation of melanocytes impairs reabsorption of cerebrospinal fluid, leading to hydrocephalia.

Diagnosis

Neurocutaneous melanosis is characterized by giant hairy pigmented nevus and multiple small melanocytic nevi. MRI head scan, lumbar puncture and ventriculography are necessary for diagnosis. Increased levels of proteins and reduced sugar levels are often found in the cerebral fluid. Melanin-containing cells may be detected.

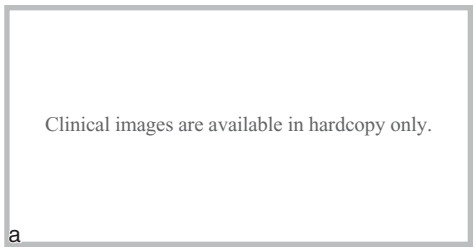
Treatment

Giant pigmented nevus is removed as completely as possible. The sooner curettage is performed after birth, the better is the result cosmetically (**Fig. 20.40-1**). Symptomatic therapy such as shunting for hydrocephalia and anti-epilepsy drugs are useful for central nervous symptoms. There is no effective treatment for melanoma of the leptomeninges.

9. LEOPARD syndrome ★

Synonym: Multiple lentigines syndrome

The main symptoms are multiple lentigines, café-au-lait spots, systemic symptoms including abnormality in cardiac transmitter function (detected by electrocardiogram), ocular hypertelorism,



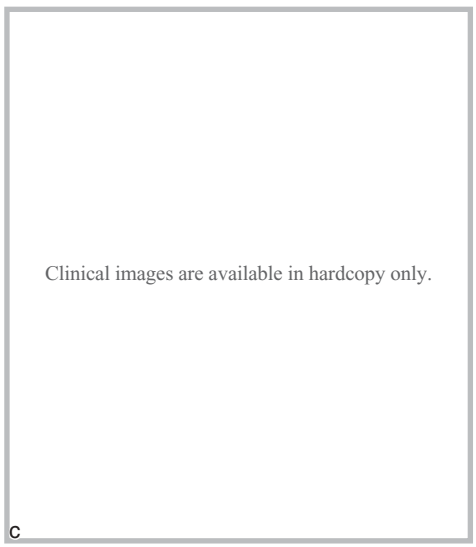
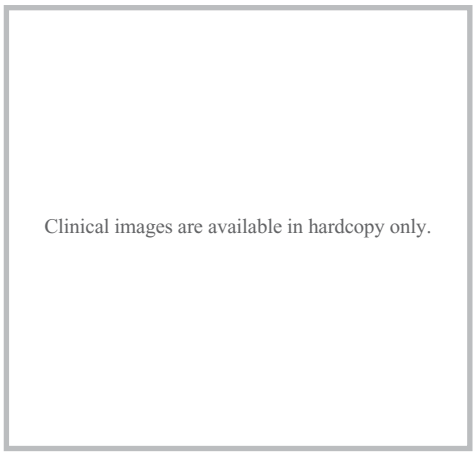


Fig. 20.40-1 Neurocutaneous melanosis.
a: On the whole body. b: It is often accompanied by nodules (arrows). c: The affected site (b) was removed.

Origin of the term LEOPARD syndrome MEMO

LEOPARD is an initialism for the following systemic symptoms: L (multiple lentigines), E (electrocardiographic conduction defects), O (ocular hypertelorism), P (pulmonary stenosis), A (abnormalities of genitalia), R (retardation of growth), D (sensorineural deafness).



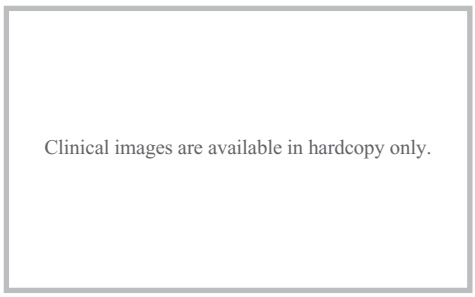


Fig. 20.40-2 Neurocutaneous melanosis.

Fig. 20.41 Nevoid basal cell carcinoma syndrome.
a: Small concavities (pitting) in the palm. b: Multiple basal cell nevi on the eyelid.

genital abnormality, stunted stature, hearing loss and mental retardation. LEOPARD syndrome is caused by mutation in the PTPN11 gene (protein-tyrosine phosphatase, nonreceptor type 11). It is thought to be autosomal dominantly inherited; nevertheless, many cases occur sporadically. Multiple lentigines are present at birth and gradually increase in number until puberty. They are comparatively small, 5 mm or less in diameter, and appear on the whole body skin. The mucous membranes are not involved. Various skin lesions, including nail malformation and skin hyperelasticity may occur. Among all lesions caused by LEOPARD syndrome, heart lesions affect the prognosis most severely.

10. Basal cell nevus syndrome ★

Synonym: Nevoid basal cell carcinoma syndrome

Multiple basal cell nevi and small depression in the palms and soles occur (**Fig. 20.41**), accompanied by multiple maxillary cysts, skeletal defects and central nervous symptoms (e.g., calcification of the cerebral dura mater, hydrocephalia, mental retardation). It is autosomal dominantly inherited. The causative gene is PTCH on chromosome 9 (9q22.3). Small multiple brown nodules of 1 mm to 2 mm in diameter are present on the whole body until the age 10. The tissue of the nodules is the same as that of basal cell carcinoma. Infiltrating lesions may form. When basal cell carcinoma is seen in young patients, basal cell nevus syndrome is suspected.

11. Von Hippel-Lindau syndrome ★★

Von Hippel-Lindau syndrome is autosomal dominantly inherited, caused by a mutation in the VHL tumor-suppressor gene on chromosome 3 (3q25). Angioma and café-au-lait spots may appear in rare cases. Multiple tumors occur throughout the body, such as renal cell carcinoma, angioblastoma in the central nerves, retinal hemangioma, pancreatic tumor and pheochromocytoma.

12. Phakomatosis pigmentovascularis ★

This is a comorbid disease of cutaneous hemangioma simplex and nevus pigmentosus. It affects the eyes, skin and central nervous system (**Fig. 20.42**). Phacomatosis pigmentovascularis, which is known to be nonhereditary, is classified into four types: port-wine stain and linear epidermal nevus (type 1), port-wine stain and dermal melanocytosis (type 2), port-wine stain and nevus spilus (type 3), and port-wine stain, dermal melanocytosis, and nevus spilus (type 4). Type 2 phacomatosis pigmentovascularis accounts for 80% of all cases. Although phacomatosis pigmentovascularis causes only cutaneous lesions, it is classified as a neurocutaneous syndrome because it is accompanied by Sturge-Weber syndrome and Klippel-Trenaunay-Weber syndrome in

about 20% of cases. Laser therapy and concealing cosmetics are useful.

13. Osler's disease ★★

Synonyms: Hereditary hemorrhagic telangiectasia, Osler-Rendu-Weber disease

Absence of elastic fibers and smooth muscles leads to telangiectasia in the arteriovenous anastomotic region. Osler's disease is autosomal dominantly inherited. Multiple papules appear on the chest, tongue, lips and palms after puberty. The papules are red at the center and are accompanied by peripheral papillary telangiectasia (**Figs. 20.43-1**, **20.43-2** and **20.44**). Mucosal bleeding, especially recurrent epistaxis, first occurs at the onset; it has diagnostic value. Broken pulmonary arteriovenous fistula may result in hemoptysis, hematothorax, gastrointestinal hemorrhage and hepatic cirrhosis.

14. Blue rubber bleb nevus syndrome ★

Multiple, elastic, rubber-ball-like blue cavernous angiomas occur in the skin and gastrointestinal tract. It is a rare autosomal dominantly inherited disease that occurs between birth and infancy, and the appearance does not change over the course of the patient's life. The angiomas vary in diameter from 2 mm to 10 cm, or sometimes larger. Gastrointestinal angioma spreads to the oral cavity, tongue and colon, leading to iron-deficiency anemia and intussusception from bleeding. Angiomas may be produced in the liver, brain, lungs, spleen, gallbladder, skeletal muscles or kidneys.

15. Maffucci syndrome

Congenital abnormality of mesoblasts causes angioma in the skin and internal organs, and ossification in the epiphyseal cartilage. Angioma is cavernous in many cases. It may be accompanied by hemangioma simplex and lymphangioma. Condroma and imperfect osteogenesis lead to bone deformity and fracture from impaired ossification of the epiphyseal cartilage.

16. Dyskeratosis congenita

Synonym: Zinsser-Cole-Engman syndrome

The onset of dyskeratosis congenita is between early childhood and puberty. More men are affected than women. The main symptoms are cutaneous reticulated pigmentation, atrophy and thinning of the nail plate, and oral leucoplakia. The onset is in late childhood. Deformity of the nail plate occurs first, followed by reticular pigmentation on the neck region spreading to the

Clinical images are available in hardcopy only.

Fig. 20.42 Phacomatosis pigmentovascularis.

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Fig. 20.43-1 Osler's disease.

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Fig. 20.43-2 Osler's disease.

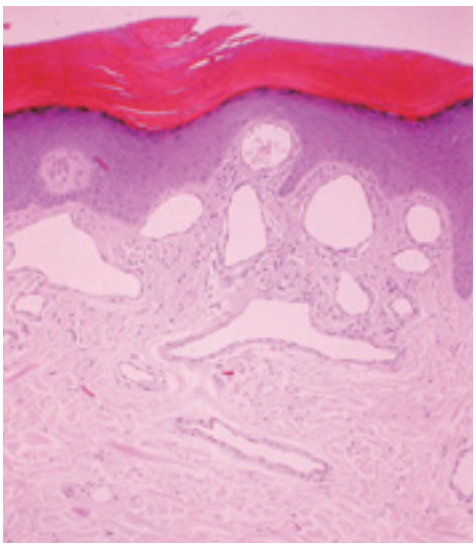

Fig. 20.44 Histopathology of Osler's disease.

trunk and extremities. Leukoderma keratosis-like change appears most frequently on the tongue, buccal mucous membranes and genitalia, and it tends to become malignant. It is accompanied by progressive aplastic anemia, splenomegaly and esophageal blockage. The main treatments are excision for leukoplakia and symptomatic therapy for anemia.

17. Epidermal nevus syndrome

Epidermal nevus syndrome is unilateral epidermal nevus accompanied by central nervous abnormalities such as mental deficiency and epilepsy, nystagmus and strabismus, bone deformity and angioma. Malignant tumor may occur as a complication.

18. Cutis marmorata telangiectasia congenita

Livedo reticularis appears at the time of birth or shortly thereafter. Telangiectasia usually accompanies it. Deformity occurs in the central nerves, heart, blood vessels, muscles, skeleton and eyes in nearly half of cases. Reticularis disappears with age, and most cases resolve within 2 years after birth. There is no difference in occurrence between sexes and races. Although it usually occurs sporadically, there are rare familial cases.