

Vitiligo and Leukoderma in Children

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Leukoderma and hypopigmentation can be a manifestation of 2 main mechanisms by which melanin might disappear from the skin. One is a dysfunction of the melanocytes; the other is loss of the melanocytes themselves. Hypopigmentation disorders can be localized or generalized. They can be either congenital/hereditary or acquired. The pattern of involvement can be circumscribed, diffuse, linear, or reticulated. Hypopigmented skin may be the only feature, the main feature, or part of a syndrome with other clinical manifestations. Recent scientific advances have provided valuable insights into the molecular basis of these diseases and a better understanding of their pathogenesis.

Pigment Cell Biology

Melanocytes are the pigment-producing cells of the skin. They reside mainly in the basal layer of the epidermis and the matrix of the hair follicle. Melanocytes are highly dendritic cells; their origin is the neural crest, from where they migrate during embryogenesis. Within the cytoplasm of the melanocytes, the melanin pigment is deposited in specific organelles named melanosomes. As the melanosomes mature and acquire melanin, they move to a perinuclear position into the dendrites. Each melanocyte interconnects with 36 keratinocytes. These surrounding keratinocytes phagocytize the tips of the melanosome-containing dendrites and transfer the pigment. This transference is essential for normal skin pigmentation.^{1,2} The differences between color in skin resides not in the number or density of melanocytes but in the activity of the individual melanocytes. In darker skin, a greater number of mature melanosomes with an increased level of melanin production is found.²

Hypopigmentation cutaneous disorders can be a consequence of different disturbances in the pigmentary system that include defects in the number or function of melanocytes, decrease melanization of melanosomes, or decrease of the transfer process from melanocytes to keratinocytes. According to the defect

present, these disorders have been classified.^{1,3} Vitiligo, piebaldism, Waardenburg syndrome (WS), tuberous sclerosis complex (TSC), nevus depigmentosus (ND), and hypomelanosis of Ito (HI) are reviewed in this article.

Vitiligo

Vitiligo is an acquired, progressive disease characterized by depigmentation of the epidermis (leukoderma) or infrequently, by partial loss of melanin (hypopigmentation). This depigmentation is a result of the destruction of pigment cells in postnatal life by mechanisms not yet well identified.⁴

Vitiligo is relatively frequent. It affects 0.5–2% of the general population, being more prominent in darker-complected people and after solar exposure.^{5,6} It usually begins in childhood or young adulthood. Approximately 30% acquire the disease before the age of 20 years and 14% before the age of 10 years; the incidence decreases in later life, and fewer than 10% develop vitiligo by the age of 42 years.⁷ The existence of “congenital vitiligo” is still unclear. Infants 4–6 months of age, however, may develop typical vitiligo mainly in the genital or perianal area (Fig 1). Some studies show a female preponderance, but this observation is not statistically significant. All races are equally affected.

In about 30% of patients with vitiligo, there is a familial clustering of cases.^{8–11} Vitiligo is not inherited, but the predisposition to have it is inherited. Some observations support an autosomal dominant inheritance with variable expression. Case reports of concordance in identical twins support a genetic basis. Control studies on human leukocyte antigens (HLA) show a positive association with HLA-DR4 (in blacks), HLA-B13 (Moroccan Jews), and HLA-B35 (Yemenite Jews).¹² Other HLA antigens have been reported (HLA-DRB4, DQB1, Dw7, DR7, DR1, etc).¹³ A mutation in the guanosine triphosphate (GTP) cyclohydrolase I gene has been described as the cause of vitiligo. GTP cyclohydrolase I is essential for the synthesis of melanin.¹⁴

Vitiligo is characterized by the destruction and absence of melanocytes in postnatal life. Pigment cells of the skin, follicles, and other extracutaneous sites are commonly involved in the destructive process. Histologic studies and histochemical and immunohistochemical stains have confirmed the absence of melanocytes in the depigmented skin and marked abnormalities in the pigment cells and keratinocytes of the spreading

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edge and at distant sites from a vitiliginous lesion. Attempts to culture melanocytes from depigmented skin have failed. The fact that glabrous skin does not respond to treatment as hairy areas do is an indirect probe of the absence of melanocytes. Follicular orifices act as a reservoir of melanocytes. Vitiligo also affects the destruction of pigment cells in other sites like the mucous membranes and eyes. Ocular pigmentary disturbances associated to vitiligo are common (15).

Etiology

There are 3 theories concerning the etiology of vitiligo. They are autoimmune, autocytotoxic, and neural hypotheses. The autoimmune theory initially developed from the association between vitiligo and autoimmune diseases (thyroid disease, adrenal insufficiency, alopecia areata, diabetes mellitus, pernicious anemia, lymphocytic malignancies, multiple myeloma, and thymoma). Subsequent research has been able to demonstrate antibodies against melanocyte surface antigens,¹⁶ common tissue,¹⁷ pigment cells,¹⁸ melanin, and tyrosinase.¹⁹

The immune mechanisms responsible for melanocyte destruction probably involve complement-dependant and antibody-dependant cellular toxicity, as vitiligo antibodies can kill melanocytes in vitro by both mechanisms.²⁰

The autocytotoxic hypothesis is based on the observation that chemicals (catechols and phenols) formed during the synthesis of melanin are cytotoxic to the cell. These chemicals are toxic to melanocytes in vitro.

Others investigators have suggested that melanin synthesis is disrupted by anomalies of the melatonin receptor. Melatonin is a natural inhibitor and modulator of melanin synthesis. A defective receptor may result in the uncontrolled production of melanin, with the release of free radicals and toxic products of melanogenesis. Abnormal activation of the melatonin receptor can occur because of an increased release of catecholamines and other neurotransmitters, because of a hereditary tendency toward expression of an increased number of melatonin receptors, or because of a dysfunction of melatonin receptors (due to intrinsic activation or via stimulating autoantibodies against the receptors). The melatonin hypothesis could explain the association of vitiligo and Graves disease, stress, neurologic/psychiatric disorders, melanoma, hereditary factors, and Koebner's phenomenon.²¹

The neural hypothesis is based mainly on circumstantial evidence. The clinical support is the distribution of segmental, dermatomal vitiligo. Others have pointed out the common origin of melanocytes as derivatives of the neural crest and the fact that certain disorders of the central nervous system are expressed in the skin with

hyperpigmentation or hypopigmentation (eg, neurofibromatosis, tuberous sclerosis).

In patients with vitiligo, depigmented areas tends to sweat less, and to have different temperature regulation, electrical resistance, and other related neural dysfunctions in the skin. An increased release of catecholamines from the autonomic nerve endings of melanocytes has been suggested.²² The potential role of a biochemical defect in the tetrahydrobiopterin pathway and/or the thioredoxin reductase system may also be involved.⁴

Clinical Features and Classification

Vitiligo is mainly a disease of young people. Depigmented patches may occur anywhere on the body, but they are most often seen on the face, backs of the hands and wrists, axillae, umbilicus, nipples, genitalia, body folds, elbows, knees, and tibial surfaces. Vitiligo is especially prominent around body orifices (eyes, nostrils, mouth, genitalia). Small patches from a few millimeters to many centimeters tend to appear first, enlarging peripherally, with new lesions appearing occasionally. Progression of the depigmentation is variable. Early or advancing lesions may be partially depigmented and may have a freckled-type appearance or multishaded hue. Later lesions become completely white. Lesions after sun exposure and after trauma, such as the Koebner phenomenon, are common. Other precipitating factors include physical injury, emotional trauma, illness, pregnancy, and drug-induced erythroderma.²³

In dark-complected people, a trichromic coloration is relatively common, with a central depigmentation, peripheral hypopigmentation, and a surrounding border of normal-pigmented skin. In 5% of patients, a pruritic, inflammatory border is associated with edema, and erythema is visible.

The skin of the scalp is commonly involved. The scalp hairs may become gray prematurely, and a few patients develop totally white hair of the scalp, eyebrows, and eyelashes. Poliosis might be present mainly in segmental vitiligo (48.6%).²⁴ The area least recognized but more often involved is the oral cavity. A good examination is essential because depigmentation in this area probably occurs in all individuals.

According to the extent of involvement and the distribution of the depigmentation, vitiligo has been categorized.^{6,8,25-27} Attempts to classify types of vitiligo have often given confusing results. A simple classification is presented in Table 1.²⁷ The localized type can be focal, with 1 or more macules in 1 area, but not clearly in a segmental or zosteriform distribution (Fig 2). The segmental type appears with 1 or more macules involving a unilateral segment of the body, ie, part of the face, part of the trunk and extremity, or 1 extremity. The lesions stop abruptly at the midline of the affected



Figure 1. Vitiligo in the perianal area

segment. Segmental vitiligo represents a particular type of vitiligo for many investigators, and it is common in younger people, with the trunk, neck, extremities, and scalp being the most common sites of involvement. It usually persists unchanged for life and is rarely associated with autoimmune disorders.²⁵ The mucosal type involves vitiligo of the mouth and mucous membranes and the genitalia. Generalized vitiligo is subdivided into 1) acrofacial, with involvement of distal parts of the extremities and face; 2) vulgaris, with scattered macules; and 3) mixed, when acrofacial and vulgaris, or segmental and acrofacial and/or vulgaris vitiligo present together. The universal type implies complete or nearly complete depigmentation.

The incidence of each type of vitiligo in this classification varies from different studies. Generalized types account for 50–90%; localized types represent ~50% of cases, with the focal type being the most common (33.7%). Segmental vitiligo always remains in this type; it does not represent a transitional stage. Very few patients have segmental and generalized types of vitiligo simultaneously.^{26,27}

Based on the severity, vitiligo can be divided into 4



Figure 2. Focal vitiligo.



Figure 3. Extensive pityriasis alba.

stages: limited (<10%) involvement, moderate (10–25%) involvement, moderately severe (26–50%) involvement, and severe disease (>50%) depigmentation. This classification is very useful to evaluate different therapeutics regimens.²⁸

Childhood Vitiligo

Very few studies have been done on the clinical spectrum of vitiligo in the pediatric population. In general, there is a female predominance; an increased frequency of a positive family history of vitiligo; a strong family history of autoimmune disorders; an increased frequency of HLA-DR5, DQW3, BfS, C4A3 and C4B1; the presence of Koebner's phenomenon; halo nevi; and premature graying. Children with vitiligo have a much higher incidence of autoantibodies than do other children, but despite this, rarely have clinical disease. In relation to the clinical types of vitiligo in children, the generalized pattern is the most common. The frequency of segmental vitiligo is also higher in children compared with adults. The most common locations for the appearance of vitiligo in children include the face and



Figure 4. Piebaldism: white forelock.

Table 1. Clinical classification of vitiligo

Localized
Focal
Segmental
Mucosal
Generalized
Acrofacial
Vulgaris
Mixed
Universal

SK Hann and JJ Nordlund.⁷

neck (50%), lower extremities (28%), trunk (18%), upper extremities (17%), and perineum (6%).^{8,29-32}

Associated Findings

A number of reports show the association of vitiligo and eye and ear disturbances. Both organs contain pigmented cells susceptible to be affected. About 40% of individuals with vitiligo will have pigmentary disturbances in the uveal tract.^{15,33} The most significant ocular abnormality is ocular inflammation or uveitis. The inflammation can be an anterior uveitis (iritocyclitis) or a posterior inflammation (chorioretinitis). The most severe form of uveitis associated with vitiligo is the Vogt-Koyanagi-Harada (VKH) syndrome.

The VKH syndrome is a multisystem disorder characterized by idiopathic uveitis, central nervous system abnormalities, and cutaneous signs, including vitiligo. It is more common in those of Asian, Hispanic, African, or American Indian descent^{34,35} and has been occasionally reported in children. Women are slightly more affected than men, and most affected patients are in the second to fifth decade at the time of diagnosis.³⁴⁻³⁷

Less severe ocular inflammation (5%), sympathetic ophthalmia, and depigmented lesions of the ocular fundus are also observed in patients with non-VKH vitiligo. Other immune disorders, like thyroid disease, diabetes mellitus, multiple myeloma, and mycosis fungoides, which are seen more frequently in vitiligo patients, can also cause visual symptoms.³⁸ Uveitis appears to be most common with vitiligo associated with cutaneous melanoma.³⁹ The ear can also be affected because pigmented cells are present in the inner ear, and sensorineural hearing loss may be seen in VKH syndrome and in non-VKH vitiligo.

Disorders of other organ systems have been associated with vitiligo. Thyroid disorders, either hyper- or hypothyroidism or thyroiditis, polyglandular dysfunction syndrome (hypoparathyroidism, chronic mucocutaneous candidiasis, and Addison's disease), adrenal dysfunction, diabetes mellitus, glucose intolerance, sarcoidosis, leprosy, pernicious anemia, various forms of lymphomas, and leukaemias have been associated with vitiligo. Many of these diseases are related to a dysfunction in the immune system, which may explain the

production of cytotoxic antibodies. With vitiligo's being a rather common disorder, it is not surprising that it has also been associated with a long list of many other organ systems abnormalities. Halo nevi, increased number of skin cancers, and metastatic melanoma have been reported associated with vitiligo. To date there is still great controversy, and epidemiologic data have not found such associations.⁴⁰⁻⁴⁵

In children and adolescents, the frequency of associated diseases is significantly less than in adults, with thyroid disease and polyglandular autoimmune syndromes being the most common associations.⁴⁰

Evolution and Psychological Impact

The onset of vitiligo is usually gradual. A rapid increase in the number of patches can occur during several months. The progression may stop, and the lesions remain for years or for life. A partial spontaneous repigmentation might occur and is common in isolated macules or patches but is rarely sufficient to be cosmetically acceptable; however, it is a good indication that therapy can be helpful.

The cosmetic disfigurement that accompanies vitiligo may have a profound effect on patient self-esteem and social relationships. Feelings of inferiority, discrimination, and embarrassment in social and sexual relations are common feelings in adults.⁴⁶⁻⁴⁸

Children start having problems with vitiligo at 5-6 years old when they enter school. The child may experience ridicule, physical embarrassment, and social isolation, but usually at this age, cosmetic appearance is of more concern to the parents than to the child. At 11-12 years, the disfigurement can be intolerable, and it is the time when they seek medical treatment. Vitiligo in children requires good support from the family, doctors, medical staff, and the community to accept the disease and to reinforce in the patient positive values to help him or her live with the disease.^{4,46}

Differential Diagnosis

The classic presentation of vitiligo as acquired, well-demarcated, depigmented, milky white patches with an absolutely normal epidermis has a very limited differential diagnosis. When the distribution of the lesions is acral, facial, or generalized, and symmetrical, segmental, or quasi-dermatomal, the diagnosis is relatively easy. There are, however, atypical clinical presentations in which the diagnosis is quite difficult, and histochemical and electron microscopy studies are needed. For some patients, however, no definite diagnosis can be made, and the evolution of the lesions is the clue for a definitive diagnosis.

The list of differential diagnosis can be divided in 2 groups. The first group is for generalized or bilateral, symmetrical leukoderma, and the second group is for

Table 2. Vitiligo differential diagnosis

Generalized or bilateral vitiligo
Genetic disorders
Piebaldism
Hypomelanosis of Ito
Tuberous sclerosis
Inflammatory/neoplastic disorders
Lupus erythematosus
Scleroderma
Sarcoidosis
Lichen sclerosis et atrophicus
Halo nevi
Pityriasis alba
Mycosis fungoides
Infectious disorders
Tinea versicolor
Treponemal infections
Leprosy
Idiopathic disorders
Idiopathic guttate hypomelanosis
Postinflammatory hypopigmentation
Segmental vitiligo
Nevus anemicus
Nevus depigmentosus
Steroid-injection-related hypomelanosis

PB Sheth.⁴⁹

segmental or unilateral, asymmetric leukoderma (Table 2).⁴⁹ Genetic disorders and ND are discussed in detail later in this article.

Lupus erythematosus can cause depigmentation in various forms. Systemic lupus might present with depigmentation plus fatigue, arthralgias, prominent nail fold capillary loops, and other symptoms. Leukoderma is more often seen in cutaneous discoid lupus erythematosus. This presents as localized, well-demarcated, erythematous, infiltrated plaques associated with epidermal atrophy, telangiectasia, and scaling. The progression of the lesions results in hypopigmentation or depigmentation with atrophy and scarring, and patients usually disclose a history of sun-induced lesions, mainly located on the face, scalp, or arms. If doubt exists, a skin biopsy and antinuclear antibody tests are helpful.

Scleroderma may present clinically as hypopigmentation in areas of sclerosis and as patches of vitiligolike depigmentation, with follicular repigmentation on a background of complete pigment loss, giving the area a "salt-and-pepper" appearance to the skin. This type of scleroderma is localized mainly to the back and upper chest, and the lesions are histologically indistinguishable from those of vitiligo. Other manifestations of scleroderma help in the diagnosis.

Sarcoidosis is rare in children. The lesions are ill-defined, hypopigmented macules scattered on the trunk and extremities; more noticeable in dark-skinned patients; and frequently associated with other cutaneous lesions or systemic findings that suggest the diag-

nosis. Histology frequently reveals sarcoidal granulomas.⁵⁰

Lichen sclerosis et atrophicus (LSA) presents in all age groups and is very common in prepubertal children, postmenopausal women, and middle-aged men. The lesion appears after a long period of pruritus, burning, and dysesthesia in the affected area. The plaques are often symmetrical, ill-defined, hypo pigmented or depigmented, and atrophic, with telangiectasias and purpura. In women, they are localized to the inner parts of the vulva, sometimes extending to the perineum and perianal area. Extragenital lesions located on the neck, shoulders, trunk, and extremities may be present. Early genital or extragenital LSA in young girls may be difficult to distinguish from vitiligo. The histology is useful. Simultaneous occurrence of genital LSA and vitiligo has been reported.^{51,52}

Halo nevi characteristically begin as well-defined, depigmented macules around a junctional or compound melanocytic nevus that advances, leaving a discrete, depigmented patch of 0.5–5 cm that is usually located on the trunk. Many lesions can occur simultaneously, and differentiation may be difficult. Histologic examination revealing melanocytic nevus cells or dense, lymphocytic mononuclear infiltrate differentiate halo nevi from vitiligo. It should also be borne in mind that both entities might present simultaneously. Halo nevi are mainly associated with segmental vitiligo; they are common in adolescents, especially those using birth control pills.²⁴ Some investigators consider halo nevi a form of vitiligo; however, the majority consider both as separate entities.

Pityriasis alba is a very common disorder usually seen in children and young adults (80–90% under the age of 15), often with a history of atopic diathesis. The lesions are hypopigmented macules, 0.5–5 cm, with ill-defined borders, slight scaliness, and variable mild erythema, generally located on the face, neck, shoulders, and extensor surfaces of the arms. In general, the differentiation from vitiligo is not difficult, but in an unusual extensive form with numerous, long-lived lesions, the differential diagnosis must be considered. Histology might be helpful in doubtful cases. In pityriasis alba, an epidermal and follicular spongiosis, focal parakeratosis, acanthosis, and superficial perivascular lymphocytic infiltrate are common findings. Ultrastructural studies may also reveal a reduced number of active melanocytes and a decreased number and size of melanosomes. Localized lesions are treated with topical steroids; extensive involvement sometimes requires UVA therapy with psoralen (PUVA)^{3,53} (Fig 3).

Mycosis fungoides is a differential diagnosis that should be ruled out in adults. The typical age range of affected patients is 30–40 years. The lesions are hypomelanotic macules with some scale or erythema, of variable size (1 cm to many centimeters), located mainly

on the trunk and extremities. Differentiation from vitiligo on a clinical basis should be straightforward; however, a biopsy to confirm the diagnosis is needed.

Infectious disorders to be differentiated from vitiligo include tinea versicolor, syphilis (secondary), and leprosy, the last 2 being very rare in children.

Tinea versicolor is a chronic infection due to *Malassezia furfur*, which may present as hyperpigmented or, more commonly, hypopigmented macules and scaly patches. It affects mainly young people between 15 and 35 years of age, with lesions localized to the chest, neck, upper arms, and back. In neonates and small children, there are cases affecting the face through transmission from infected parents. The diagnosis is easy using a Wood's lamp (yellow fluorescence), and KOH staining reveals hyphae and spores. Nonactive lesions might need a histochemical and electron microscopy examination to confirm the diagnosis, showing the presence of melanocytes in lesional skin.⁵⁴

In endemic areas, **leprosy** caused by *Mycobacterium leprae* can present clinically with hypopigmented lesions with a morphology dependent on the type of leprosy. Associated erythematous, well- or ill-defined patches, and indurated plaques are present. Most lesions have a partial or complete loss of sensation of temperature, touch, and pain. The clinical picture and histology, with compact granulomas around the nerves or diffuse granulomatous inflammation with foamy macrophages, help in the diagnosis.⁵⁵

Idiopathic guttata hypomelanosis is a disorder of adulthood. Lesions are well-circumscribed, sharply defined, oval or round, polygonal, hypopigmented or depigmented areas of very small size (2–5 mm up to 1 cm). They are localized mainly on the extremities and are related to sun exposure. The age of onset, clinical presentation, slow progressive nature, lack of confluence, and absence of depigmented hairs differentiate these entities from vitiligo. If necessary, histology and biochemical studies can be done.

Although unlikely, hypopigmentation secondary to exposure to products containing catechols and phenols, such as germicides or after using toothpaste containing cinnamic aldehyde, may occur as a chemically induced vitiligo. Hypopigmentation secondary to cutaneous disorders resolve, like psoriasis, varicella, and atopic dermatitis. Intralesional corticosteroid therapy can induce hypopigmentation in a focal distribution. Usually, the history, pattern, and ill-defined borders of the lesion help in the diagnosis.^{49,55}

Treatment

Treatment is empirical and often difficult. Children demonstrate an enhanced therapeutic response to different modalities compared with adults.²⁹ The options for therapy are dependent on the age, location, and

extent of the disease. All forms of therapy require time (a minimum 3 months) and a reservoir of melanocytes (usually from the outer root sheath of hair follicles).

Vitiligo is an asymptomatic disease, and many children with minimally affected skin do not want any treatment. There is no evidence that early treatment of minimal disease will alter the natural history. All patients should be counseled to avoid sun exposure and to use sunscreen.

Topical Steroids

In children <2 years of age, treatment with medium-potency steroids, applied 1 or 2 times a day for 1 or 2 months and then tapered to a lower-potency steroid, is indicated. In older children, treatment can be initiated with a superpotent topical steroid. Patients must be monitored for side effects. Also, short courses of systemic steroids are indicated in patients with rapidly progressive disease.

Topical PUVA

Topically applied PUVA can be used safely in children. It has the advantage of avoiding the systemic side effects of psoralens, but it requires a very motivated and compliant patient and family. This modality is indicated for patients with <20–25% involvement. Concentrations of 0.01% or 0.1% Oxsoralen ointment plus UVA in increasing doses in a very careful technique can be used. A mean repigmentation rate of 58% has been reported with this treatment.⁵⁷

In patients with <10% involvement, another option is PUVASOL (topical psoralens + sunlight). The concentration of Oxsoralen ointment should not be greater than 0.001% combined with 15–30 minutes of sunlight exposure (between 10 AM and 4 PM). This treatment is easier, less expensive, and a good option to be employed in sunny weather. Reports of mean repigmentation obtained are 71%.⁵⁷ Side effects are minimal.

L-Phenylalanine

Variable results have been reported with oral and topical L-phenylalanine with UV light in children and adults.⁵⁸ The exact mechanism of action is unknown. L-Phenylalanine is an essential amino acid, the precursor of tyrosine, that apparently alters the Langerhans cells and inhibits antibody production. Recommended dosages are 50 mg/kg or a maximum of 2 g per day. The usual initial dose is 500 mg plus sun exposure at noon for 5–10 minutes. In case of lack of response, the dose is increased after 2 months. L-Phenylalanine is contraindicated in patients with phenylketonuria, liver or renal dysfunction, skin cancer, arsenic exposure, before radiation therapy, pregnancy, and lactation.⁵⁹

Systemic PUVA

Oral psoralens are not used before 9 years of age and are reserved for patients with moderate to severe disease involving >20–25% of the cutaneous surface. The standard dose of 8-Methoxypsoralen is usually 0.2 to 0.4 mg/kg. Treatment must be continued for 4 to 6 months to see if any repigmentation develops. Ocular toxicity, long-term risk of skin cancer, and other minor side effects are complications of the treatment.⁶⁰ Psoralen plus sunlight has also been used but requires careful supervision to limit the risk of sunburn. The combination of PUVA and topical calcipotriol has been successful in refractory cases.⁶¹

UVB Phototherapy

Recent reports of narrow-band UVB (311-nm) therapy have shown its efficacy and safety compared to PUVA.^{62,63}

Other treatment modalities include vitamin supplementation (B complex, E, and C),²⁸ camouflage and dyes helpful in children with small lesions, tattooing, pseudocatalase calcium cream and UVB,⁶⁴ oral and topical khellin,⁶⁵ topical melagenina,⁶⁶ microphotoenergetic UVB rays and immunomodulators (levamisole, isoprinosine, cyclosporine, cyclophosphamide, nitrogen mustard, and others). Depigmentation with monobenzyloxy ether of hydroquinone is a viable therapy for patients with >50% cutaneous depigmentation but is rarely used in children and young adults.

Surgical Therapies

Transplantation of the epidermis, autologous suction-blister grafts, autologous punch grafts, and autologous melanocyte transplant are some of the possible surgical procedures that should be practiced only on teenagers or adults.

Piebaldism

Piebaldism is a congenital disorder of hypopigmentation characterized by a white forelock in association with hypopigmented macules and patches. In general, lesions are stable in size and increase in proportion to the child's growth. The lesions are mainly located on the anterior trunk, mid-portions of the extremities, mid-forehead, and frontal scalp. Hyperpigmented macules are present in normal skin and within the areas of leukoderma. The distribution and pattern of pigmentation are very characteristic.^{67,68}

Piebaldism is an inherited disorder, autosomal dominant, with a high degree of penetrance. A mutation in 1 of the 2 copies of the proto-oncogene KIT located on chromosome 4 has been described.⁶⁹

Histopathologic and electron microscopic examinations of hypopigmented skin or hair follicles of the white forelock show the complete absence of melanin and melanocytes or a reduced density. When melano-

cytes are seen, they are morphologically abnormal, with spherical, granular melanosomes.⁷⁰ In the hyperpigmented macules, a normal number of melanocytes and an abundance of melanosomes in melanocytes and keratinocytes are found. The most classic clinical finding in piebaldism is the frontal white forelock, a tuft of white hairs over the mid-frontal scalp found in 80–90% of patients (Fig 4). This is often V-shaped and associated with the loss of pigment in the underlying scalp. Poliosis of the eyebrows and eyelashes and premature graying of scalp hair may be present. The other hypomelanotic areas are characteristically distributed over the forehead, neck, anterior trunk, flanks, and mid-portion of the extremities (Fig 5). Typically spared are the central back, shoulders, hips, hands, and feet, which helps to differentiate it from vitiligo. The affected areas are milky white on Wood's lamp examination. Often, hyperpigmented or normally pigmented macules and patches are present within the areas of leukoderma and in uninvolved skin. They represent cafe au lait macules, and their presence does not mean that the patient also has neurofibromatosis.^{67,68,71}

Individual cases of piebaldism have been associated with mental retardation, cerebellar ataxia, short stature, Hirschprung's disease, chondrodysplasia, pulmonic stenosis, and heterochromia irides.⁷²

The differential diagnosis of piebaldism includes vitiligo, which differs from piebaldism because it is an acquired and progressive disorder rather than a congenital and stable one, and the areas of involvement are different. The major entities for a differential diagnosis are the piebaldism syndromes associated with deafness (Woolf syndrome) or with facial dysmorphism (WS). Because of the presence of deafness in these 2 syndromes, patients with piebaldism should routinely have auditory testing. Piebaldism should also be differentiated from Ziprkowski-Margolis syndrome or albinism-deafness syndrome. This is characterized by a diffuse, pigmentary dilution of hair-skin, with the exception of the buttocks and genital region, plus hyperpigmentation with a leopardlike appearance, deaf-mutism, and heterochromia irides. The clinical appearance differs considerably from piebaldism, and the mode of inheritance is recessive (gene mapped to Xq 26.3–27.1).⁷² Scalp poliosis should be differentiated, with a large group of diseases associated with this particular finding.

No treatment is available for piebaldism. Sunscreens should be applied to the hypopigmented areas. Mini-grafts transplantation of uninvolved skin into areas of leukoderma have been successful.⁷³

Waardenburg Syndrome

WS is an autosomal dominant disorder described in 1951 and characterized by a white forelock (present in



Figure 5. Piebaldism: typical skin lesions.

17% of patients) and skin lesions of piebaldism (12%), increased distance between the inner canthi with normal interpupillary distance (dystopia canthorum), a broad nasal root, hypertrichosis and fusion of the medial eyebrows, heterochromia irides, and congenital sensorineural hearing loss (Fig 6). Three types of WS have been described. WS I and II are mainly differentiated by the presence or not of dystopia canthorum. Other ocular findings can be present (dystrophy of the lacrimal puncta, blepharophimosis, hypopigmentation of the fundus). Type III (Klein-Waardenburg syndrome) is associated with congenital musculoskeletal anomalies, mainly of the upper limbs (hypoplasia of muscles, flexion contractures, fusion of carpal bones, syndactyly).^{68,72,73,74}

Mutations in the *PAX-3* gene on chromosome 2q



Figure 6. Waardenburg syndrome type II.



Figure 7. Nevus depigmentosus, systematized form.

35–37 for WS types I and III and mutations of the microphthalmic transcription factor gene on chromosome 3p13 for WS II have been reported.⁷²

Poliosis of the eyebrows and eyelashes, premature graying of the scalp hair, and palmoplantar keratoderma might be present. The white forelock and the leukodermic patches can be less noticeable with age. Other associated findings include Hirschsprung's disease, facial clefts, congenital heart defects, and myelomeningocele.⁷⁵

WS should be differentiated from other syndromes related to hearing loss. Woolf syndrome, originally described in 2 American Indian brothers, is a piebaldism plus congenital sensorineural hearing loss without any other features of WS. Patients with VKH syndrome associated with vitiligo might have decreased hearing. Dystopia canthorum is also seen in the oral digital-type I syndrome. The prognosis of WS is dependent on the severity of the associated deafness and the presence of anomalies.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC), also named Bourneville's disease, Pringle's disease, or epiloia, is an



Figure 8. Hypomelanosis of Ito.

autosomal dominant inherited condition with a high mutation rate of ~65%. The prevalence ranges from 1 in 6000 to 1 in 170,000 inhabitants in various populations. Two gene loci have been identified for TSC, on chromosome 9q34 (*TSC1*) and on chromosome 16p13 (*TSC2*). These 2 linkages occur in ~90% of patients with TSC. The genetic heterogeneity may explain the variability in clinical manifestations in TSC.⁷⁶

Involvement of all organs, except muscle and the peripheral nervous system, has been reported in TSC. The skin lesions often provide the clue to the diagnosis: cutaneous hamartomas are pathognomonic of TSC and include forehead plaques, hypomelanotic macules, shagreen patches, facial angiofibromas, and periungual fibromas.

Forehead plaques may be present at birth or appear shortly afterward, and the common first sign is as a soft, red plaque on the face, neck, or scalp. Shagreen patches are yellow to orange, raised, firm, and fleshy, usually located on the trunk. Periungual fibromas appear at puberty or thereafter as a smooth, firm, clove-shaped tumors around the nail plate. Facial angiofibromas are rarely obvious before the age of 2 years and are flesh-colored to brown, small papules located on the midportion of the face; these occur in 47–90% of patients. Hypomelanotic macules, present at birth but occasionally developed later, are usually several lesions located on the trunk and limbs. These can be localized macules or patches of any shape from oval, lance-ovate, polygonal, to an ash leaf configuration, with a size range between 1 and 3 cm. Once they appear, they remain stable in size and shape. Rarely, confettilike lesions 2–4 mm in size are seen, mainly in young adults on the arms and legs, or a segmental distribution may be present. All of these hypomelanotic macules reflect light because of the absence of melanin, so the use of a UV lamp is helpful in their detection. The number of hypopigmented macules can vary from 1 to >100. Fifty percent of patients have 5 or fewer, and 11% have only 1 lesion. These are considered part of the secondary diagnostic criteria. Histologically, these lesions have normal numbers of melanocytes but an absence of melanosomes.⁷⁶ Poliosis of the scalp, eyebrows, eyelashes, and pubic and body hair is also seen, as well as circumscribed hypopigmentation of the iris or fundus.

Central nervous system involvement is common in TSC and includes infantile spasms, seizures, learning and behavioral problems, focal neurological deficits, multiple cortical tubers, subependymal glial nodules, and cerebral calcifications. Retinal astrocytomas are present in 25% of affected individuals, are usually asymptomatic, and are also of diagnostic importance. Cardiac rhabdomyomas can be seen as early as the second trimester of pregnancy and are present in 60% of affected individuals. Dental enamel pits are a highly specific sign of TSC, especially in adult patients. He-

matic, renal hamartoma, and lung involvement is common.^{77,78}

The diagnosis is made on a clinical basis. Diagnostic criteria for the disease, based on a combination of primary, secondary, and tertiary features, have been defined.^{79,80} Radiologic confirmation of the intracranial lesions is useful in evaluation of patients. CT scans demonstrate intracranial nodules. The MRI scan is the best method to detect cortical tubers and localize more accurately the brain lesions. The differential diagnosis of hypopigmented macules includes nevus anemicus, vitiligo, ND, and idiopathic guttate hypomelanosis.

Management of these patients is related to the different clinical manifestations. Hamartomas (most commonly renal) can be excised. Infantile spasms are treated with corticotropin injections. Recurrent seizures are usually associated with subnormal intelligence. Approximately 20% of patients die before 30 years of age. First-degree relatives of patients of TSC can be diagnosed through radiologic screening in 7–15% of cases.

Nevus Depigmentosus

ND is defined as a congenital, nonprogressive, well-circumscribed macule or patch of hypopigmentation, stable in size and shape throughout life. Although present at birth, the hypopigmented area may go unnoticed for the first months of life and be clinically apparent later in life in children with light skin. There are not hyperpigmented borders around the achromic area (clinical diagnostic criteria Coupe 1976).⁸¹ Both sexes are equally affected. The pathophysiology is probably associated with a clone of cells that have reduced melanogenic potential and that arises primarily via a postzygotic somatic mutation. Inheritance for ND has not been determined.

The histologic findings by light microscopy show a normal or decreased number of melanocytes. Electron microscopy can detect a large reduction in the number of melanosomes and aggregated melanosomes of variable morphology. A decrease in the synthesis and transfer of melanosomes has been observed; however, the size and degree of melanization of the melanosomes are normal.⁸²

ND is present in approximately 1 in 130 newborns.⁸³ Clinically, an ND in the majority of cases is an isolated, uniformly hypopigmented, but not completely depigmented, area that becomes more noticeable with Wood's lamp examination. The majority of lesions are <6 cm² in size. They are rectangular, oval, or polygonal, with irregular, serrated borders except at the midline. Solitary lesions are most commonly seen on the trunk (44.8%) or proximal extremities, but the head and neck may be also sites of involvement. There are 3 different forms of ND: isolated, segmental, and systematized (unilateral whorls and streaks) (Fig 7). The isolated

form is by far the most common (59.7%), and as a rule, the lesions do not cross the midline.⁸³ Hair within an ND may also be hypopigmented. Poliosis can be present (6%). Lentiginosities might develop within the ND. Systemic manifestations associated with ND are rare; 3 patients with unilateral hypertrophy of the extremities on the involved side and 1 patient with seizures and mental retardation have been reported.^{84,85}

The differential diagnosis of ND includes a list of entities. Nevus anemicus is a localized area of vasoconstriction whose borders are obscured by diascopy, distinguished from focal, segmental vitiligo, which is an acquired, localized area of complete pigment loss. Lesions of segmental vitiligo are relatively stable but show no melanocytes on histopathologic examination. The ash leaf spots of TSC can be easily confused with the isolated or the segmental form of ND, but can be distinguished only by the presence in TSC of other cutaneous signs and by the systemic involvement. Sometimes electron microscopy examination can help, showing small and poorly melanized melanosomes. When linear streaks or a blocklike configuration of hypomelanosis is present, the major differential diagnosis is HI, a neurocutaneous disorder characterized by unilateral or bilateral, hypopigmented streaks and swirls that follow Blaschko's lines and that are associated with ocular, musculoskeletal, and central nervous system abnormalities; however, if systemic abnormalities are absent, then the differential diagnosis can be quite difficult. The fourth stage of incontinentia pigmenti, which appears late in life, may be considered in the differential diagnosis in adults. Children with ataxia-telangiectasia may have hypomelanotic macules in addition to telangiectasias, premature graying and café au lait macules. In female carriers of Menke's kinky hair syndrome, an X-linked recessive disorder related to dysfunction of a copper-transporting protein, streaks and swirls of hypopigmentation are present in the skin, plus patches of pili torti in the scalp. Rarely, the differential diagnosis of ND needs to be made with other conditions associated with hypopigmentation following Blaschko lines (ie, lichen striatus, epidermal nevus, linear keratosis follicularis).^{81,86,87}

There is no effective treatment for this disorder. Cosmetic cover-up may be a good recommendation. Partial repigmentation with autologous melanocyte grafting has been used.⁸⁸

Hypomelanosis of ITO

First described in 1952 under the name of incontinentia pigmenti achromians, it is nowadays considered under the group of genetic mosaicism.⁸⁷ HI is clinically present as a neurocutaneous syndrome, with 62–94% associated with abnormal systemic features. The prev-

alence of the disease is ~1 in 800 children in a general pediatric hospital.⁸⁹

Skin pigmentation is the hallmark of HI. The hypopigmented macules in a whorled and streaked marblecake configuration, usually bilateral, are present mainly on the trunk and extremities. These narrow bands follow the lines of Blaschko and occasionally can have a blocklike configuration (cutaneous pattern of mosaicism). They may be present at birth or gradually appear during infancy or childhood (Fig 8).

Histopathologic examination of the hypopigmented skin reveals either a normal or a decreased number of melanocytes and melanosomes. A decrease in the melanin content is also present. There are no inflammatory cells in the dermis, and no pigment incontinence is found. Other ectodermal defects are scalp abnormalities (alopecia, unilateral coarse and curly hair), high-arched palate, and teeth alterations (conical teeth, partial anodontia, dental dysplasia and hypoplasia, enamel alterations).

About two thirds of patients with HI have neurologic, musculoskeletal, and ocular abnormalities. The most common neurologic symptoms are mental retardation, seizures, and motor deficits, whereas musculoskeletal findings include craniofacial dysmorphism, scoliosis, and thoracic and finger deformities. The most common ocular anomalies are strabismus, nystagmus, scleral melanosis, myopia, congenital cataract, amaurosis, and dacryostenosis. Cardiac, renal, and urethral alterations have been described.^{89–92}

The differential diagnosis of HI includes all linear lesions that follow the lines of Blaschko, the most common being the fourth stage of incontinentia pigmenti, Goltz syndrome, and the systematized form of ND.^{78,87,93}

Incontinentia pigmenti in its fourth stage might leave hypopigmented lesions, usually in the extremities, in adults. The eruption is usually preceded by the vesicobullous, verrucous, and hyperpigmented stages. There are also ectodermal, neurologic, and musculoskeletal abnormalities. The histopathologic examination shows the absence of eccrine glands and hair follicles. In the Goltz syndrome, also called focal dermal hypoplasia, bands of hypopigmentation associated with the linear areas of telangiectasias, dermal atrophy with fat herniation, hyperpigmentation, periorificial papillomas, nail dystrophy, and focal alopecia help in the clinical differential diagnosis. Additional musculoskeletal, eye, and tooth alterations are present. The systematized form of ND is the most important differential diagnosis. Mosaicism may be the presumed underlying etiology for both clinical pictures. ND, however, is a congenital, stable leukoderma, not associated with systemic manifestations.

Table 3. Clinical approach in the diagnosis of leucodermas in children

History and examination	
Age of onset	At birth, during infancy, later
Progression of disease	Slow, rapid, stationary
Pattern	Localized, generalized, systematized
Precipitating factors	Trauma, sunburn, stress, chronic illness, etc
Family history	Similar disease, ethnic origin, consanguinity, etc
Sites affected	Skin, scalp, body hair, eyebrows, etc
Associated cutaneous changes	Keratoderma, poliosis, shagreen patches, scaliness, loss of sensitivity or temperature, etc
Associated systemic manifestations	Nails and teeth abnormalities, ocular, central nervous system, renal, musculoskeletal anomalies, etc
Skin, hair, and mucous membranes examination	Leukoderma, café-au-lait spots, erythema, atrophy, telangiectasias, mucous tumors, papillomas, etc
Investigations	Wood's lamp, skin scraping (KOH smear), skin biopsy, genetic studies, MRI, CT scan, others

Conclusions

Leukodermas in children are due to a great variety of causes, of which ND and vitiligo are among the most common. It is sometimes very difficult to propose a diagnosis. Table 3 summarizes the important points in the history and examination, plus certain investigations that may help in the differential diagnosis.

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