ELSEVIER

Cutaneous Manifestation of Internal Diseases in Infants and Children

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Cutaneous manifestations of systemic diseases occur very often and are sometimes difficult to diagnose. Dermatologists and internists must be aware of the signs and symptoms of these associations so that they can make early diagnosis, thus preventing, in some cases, the progression to a severe and fatal disease. In this article, collagen vascular diseases such as scleroderma, dermatomyositis, and lupus erythematosus, kwashiorkor, acrodermatitis enteropathica, lipoidoproteinosis, phenylketonuria, skin signs of diabetes mellitus, and diseases of the thyroid and adrenals, as they are related to infants and children, will be discussed.

Collagen Vascular Diseases

Collagen vascular diseases comprise a group of conditions more common in adults that may affect skin, connective tissue, and internal organs. When seen in children, however, these diseases are usually accompanied by significant morbidity and present different special clinical manifestations.[1] Scleroderma, dermatomyositis, and lupus erythematosus, the most prevalent manifestations of collagen disorders in children, will be reviewed.

Scleroderma

Scleroderma, or morphea, is a chronic connective tissue disorder characterized by hardening of the skin and depicts a spectrum of clinical presentations. It is more frequent and severe in adults; localized and skin-confined forms predominate in children.[1,2]

The hallmark of scleroderma is the deposition of excessive amounts of collagen in the skin and internal organs; however, the precise pathogenic mechanisms involved in the etiology of the disease are uncertain.[2] There is reference to *Borrelia* infections, bacille Calmette-Guérin (BCG) vaccination, trauma, and use of some drugs as triggering factors, but no firm evidence has been forthcoming.[3,4] Studies suggest that there is an increase in the amount of the enzyme lysyl oxidase in the lower dermis and subcutaneous of scleroderma patients; this enzyme is responsible for the cross-linking of collagen fibers and probably accounts for the thickening of cutaneous structures.[5] Other hypotheses are related to increased expression of adhesion molecules after endothelial injury.[2]

The outcome of scleroderma depends on the type, extension, and specific organ or tissue involvement. Many cases progress with high morbidity, but others constitute just a cosmetic problem.[3] The disease course in infants and adolescents was demonstrated to differ from that in adults.[6]

Localized Scleroderma

Localized scleroderma is a limited fibrosis usually restricted to the skin and superficial structures.[7] Vasospasms and internal organ involvement are absent, and the morbidity is determined mainly by disabling defects due to skin, joint, and muscle compromising.

Morphea is the most common form in children (Fig 1 and Fig 2). Lesions are asymptomatic, unique or in small numbers, and usually start with a violaceous or erythema discoloration. They gradually assume a hard consistency and become ivory or hypochromic, with atrophy of the subcutaneous tissues that takes 3 to 5 years to resolve.[3,8] Predilection zones are the trunk and legs.

Special forms are the guttate morphea, with small, multiple, hypopigmented papules with minimal sclerosis, usually localized in the neck, shoulders, and anterior chest.[3] Generalized morphea is a more severe form, determining contractures and ulcers with a chronic course without signs of spontaneous resolution. Typical of infancy is the very aggressive diffuse scleroderma referred to as pansclerotic morphea of childhood.[6]

Linear scleroderma is characterized by bands of sclerosis, often in a dermatomal distribution. When crossing the joints, lesions are usually associated with atrophy of subjacent structures such as muscle, bone, and synovium, leading to growth defects, the severity of

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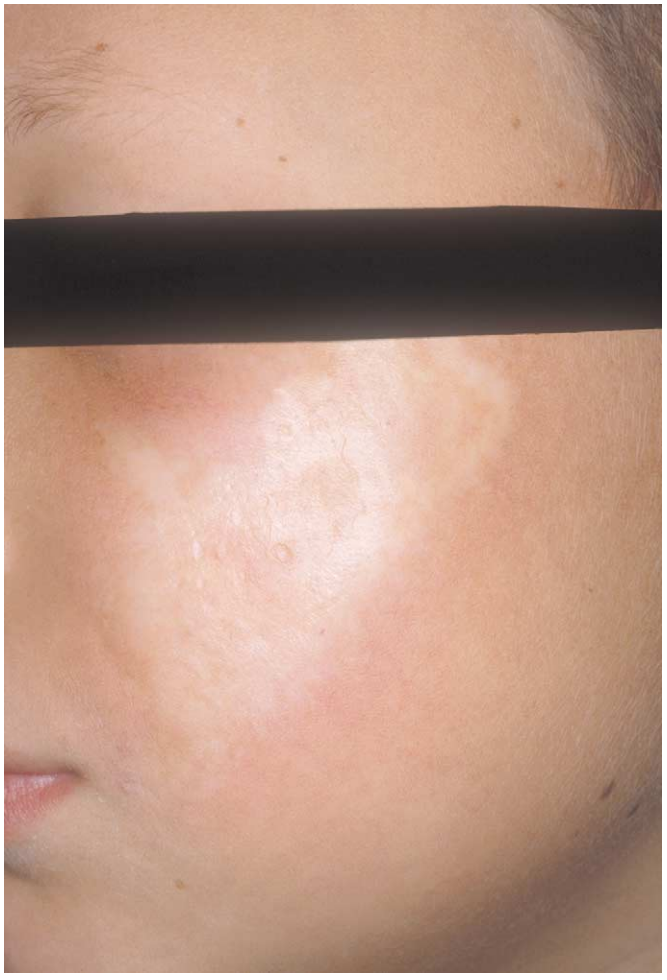

Figure 1. *Morphea—hypochromic patch with atrophy on the face.*

which depends on the affected zone.[3] Scleroderma *en coup de sabre* is a descriptive term for lesions affecting the face or scalp (Fig 3). This variant is very disfiguring, with loss of hair and eyelashes and facial asymmetry;

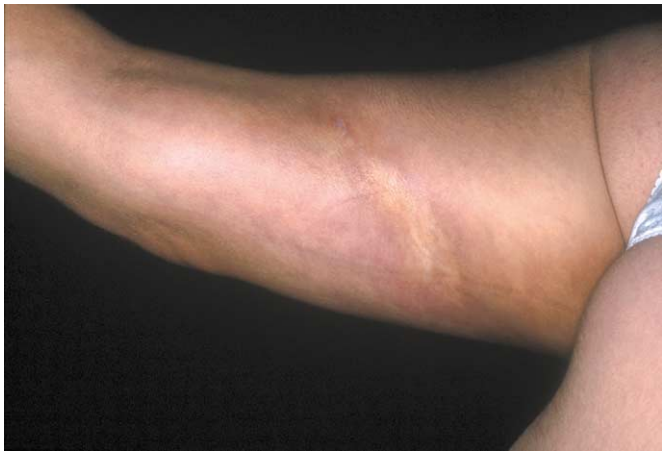

Figure 2. *Morphea—hypochromic patch showing hard consistency, with atrophy of the subcutaneous tissues on the arm.*

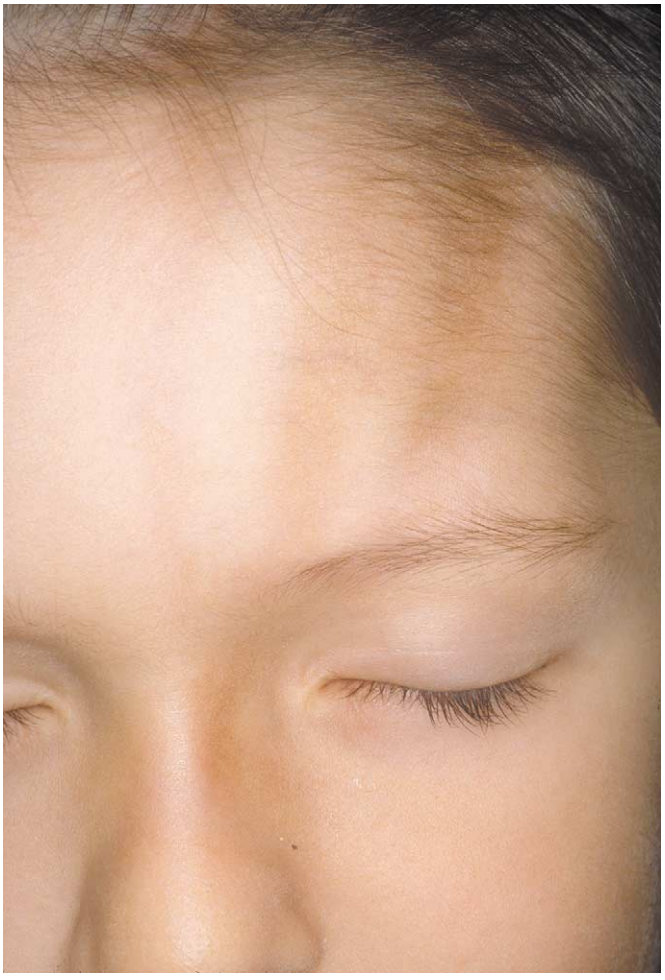

Figure 3. *Scleroderma* en coup de sabre *on the face.*

some cases also present vascular abnormalities of the brain and morphea lesions in other areas. The Parry-Romberg syndrome, comprising paramedian atrophy without induration involving the mandible and tongue, is sometimes regarded as a severe form of linear scleroderma (Fig 4 and Fig 5).[8]

Many treatments were proposed for localized scleroderma, and none are really effective. Psychological support and adequate physiotherapy are fundamental, especially for the linear and generalized forms. Anti-inflammatory drugs, low-dose corticosteroids, and D-penicillamine may be tried in rapidly progressive disease.[1,9] Good results are described with photochemotherapy, based on the increase of collagenase activity in human skin induced by UVA radiation.[10,11]

Progressive Systemic Sclerosis

The progressive form of systemic sclerosis is very rare in childhood, and, due to its rarity, the diagnosis is almost always delayed.[2] The onset of the disease is gradual and usually starts by Raynaud's phenomenon in 70% of patients. This vascular symptom is very un-

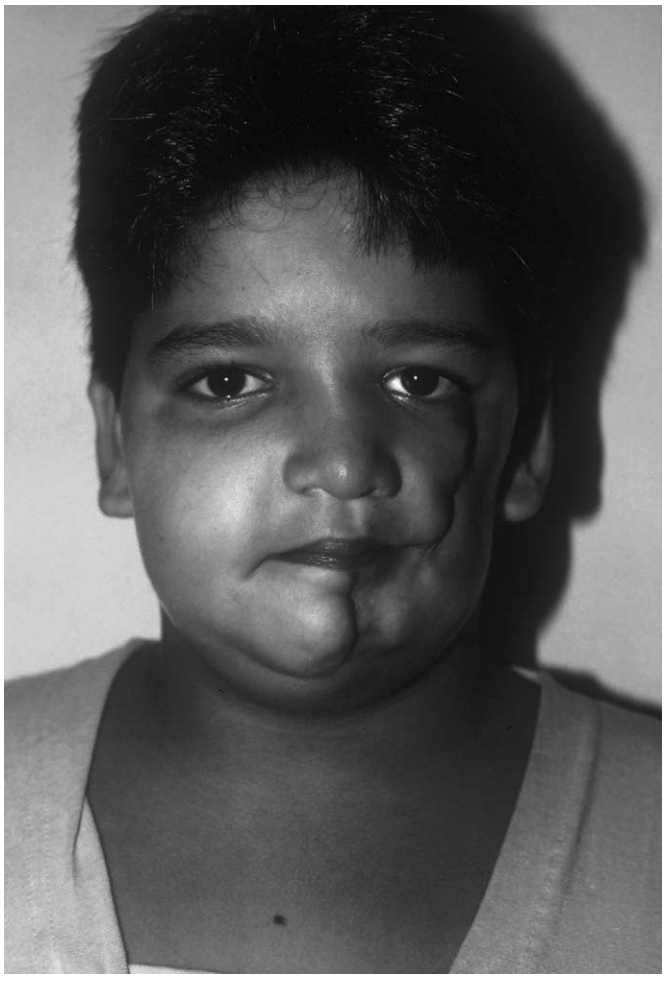

Figure 4. *Parry-Romberg syndrome—considered a severe form of linear scleroderma. (same patient as in Fig 4)*

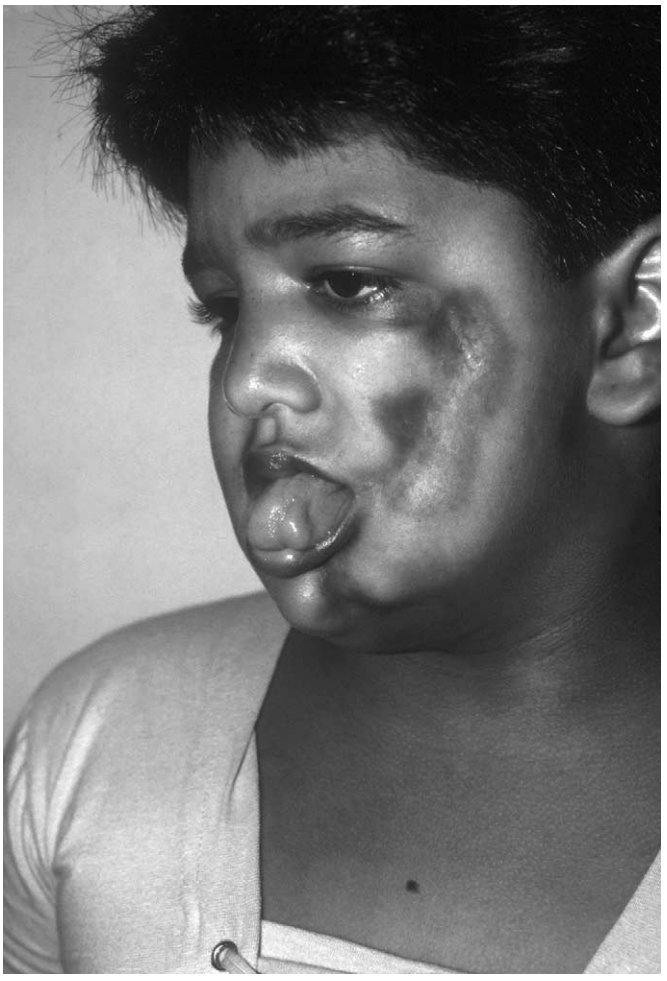

Figure 5. *Parry-Romberg syndrome—paramedian atrophy without induration involving the mandible and tongue. (same patient as in Fig 3)*

common in children and usually reflects the presence of collagen vascular disease.[1,8] Furthermore, young patients show a different antibody profile when compared with adults: anticentromeric protein antibodies are rarely positive, in opposition of localized forms, where they are frequently detected; antinuclear antibodies are not quite characteristic, being marked positive just in the cases associated with extensive cutaneous lesions.[3] Twenty percent to 40% of the patients with diffuse cutaneous and pulmonary disease have antibodies to topoisomerase-1 (anti-Scl 70), and they also have anti-RNA polymerase III (RNAP III) antibodies.[1,2,7]

Visceral involvement determines the prognosis of the disease. Cardiac, renal, and gastrointestinal systems are mainly affected because of the endothelial damage, microvascular obliteration, and overproduction of connective tissue proteins.[2,3]

Clinically, systemic sclerosis could be classified into three subtypes, according to clinical features, progression of the disease, and laboratory abnormalities: limited cutaneous systemic sclerosis, diffuse systemic sclerosis, and overlap syndromes. The first form presents with Raynaud's phenomenon, digital pitting scars, pulp atrophy, terminal bone tuft reabsorption, calcinosis, telangiectasia, and ischemia; sclerosis involves the fingers, eventually extending to the hands and forearms, face, and feet. The face takes on an expressionless appearance, with loss of skin wrinkles, tight lips, and inability to fully open the mouth. The esophagus is frequently affected, and pulmonary hypertension is rare. The most important disabilities are determined by contractures and vascular insufficiency.[3,7] Diffuse systemic sclerosis in children is similar to the adult form: skin lesions begin with strong inflammatory reaction and edema of extremities before the installation of sclerosis. Arthralgias are intense, mimicking juvenile arthritis, but visceral compromise is asymptomatic in the majority of cases. Esophageal dysmotility is usually the first general complain and later, muscle weakness, weight loss, fatigue, and pulmonary, renal, and cardiac disease appear.[7] Overlap syndromes are characterized by the development of signs of several connective tissue diseases such as polymyositis, dermatomyositis, systemic lupus

erythematosus, rheumatoid arthritis, and scleroderma, concomitantly or in different stages of the disease.[2,12]

The concept of persistence of maternal cells in patients with systemic scleroderma remains pathogenetically fascinating, as does the resemblance with graft-versus-host-disease.[6]

The therapeutic approach to systemic sclerosis depends on the stage of the disease and should be directed toward the management of vasospasms, inflammation, fibrosis, and organ involvement. In patients with Raynaud's phenomenon, cold protection is mandatory; topical nitroglycerin and nifedipine are also indicated. Nonsteroidal anti-inflammatory drugs help in the management of pain and inflammatory symptoms. Steroids are useful for myositis and interstitial lung disease but may precipitate renal failure. D-Penicillamine has a good effect on sclerosis. The dosage is 3 mg/kg/d in the first 2 months, increasing monthly to a maximum of 15 mg/kg/d. Methotrexate and interferon-alfa are alternatives for D-penicillamine and act more rapidly.[3] Other modalities of treatment include cyclosporine, colchicine, cyclophosphamide, extracorporeal photochemotherapy, and plasmapheresis.[13–16] In view of new therapeutic options, controlled trials have not established a "gold standard" for treatment, but autologous bone marrow transplantation may be considered rescue therapy for selected patients.[6] Treatment must be individualized to the patient and his or her specific limitations brought about by the disease. Early diagnosis, supportive care, and physical therapy combined with early orthopedic surgical intervention to release joint contractures are among the most efficacious treatments.[17]

Dermatomyositis

Dermatomyositis is a rare, idiopathic inflammatory myopathy, affecting mainly women, with the greatest incidence between 5 and 14 years of age, in the juvenile form.[1,18,19] It is characterized by inflammation, necrosis and gradual regeneration of muscle fibers, skin lesions, and systemic manifestations such as fever, lethargy, and general discomfort.[20] The diagnosis is based on the fulfillment of the Bohan and Peter criteria that comprise clinical features, elevation of serum muscle enzymes, compatible electromyography, and muscle biopsy histology.[21] The microvasculature seems to be the primary site of pathological alterations, possibly caused by immune complex deposition, activation of terminal complement components, release of cytotoxic factors from mononuclear cells, organ-specific autoantibodies, and infectious agents such as enterovirus.[20,22–24]

Dermatomyositis is classified into two forms: type I, which is rapidly progressive with high mortality in the first year of diagnosis, and type II, much more common and clinically similar to the adult form, except for the frequency of dystrophic calcinosis and rare association with malignancies.[1,19]

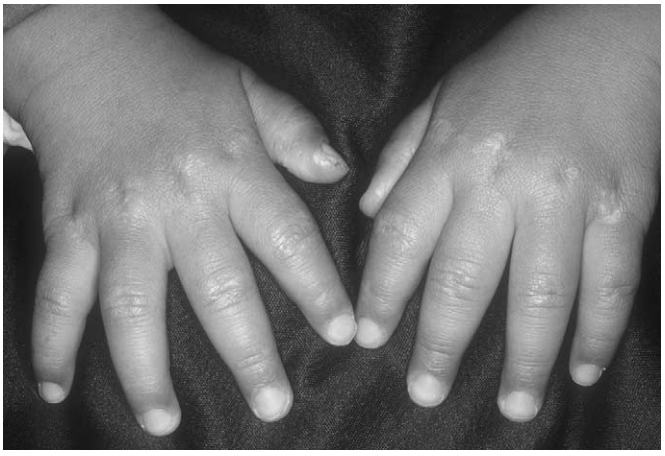

Figure 6. *Dermatomyositis—telangiectatic papules over the interphalangeal joints (Gottron's papules).*

The onset of the disease may be acute; however, it is usually slow and insidious. The first symptom is most often a photosensitive pink to lilac edematous malar and eyelid eruption, called heliotrope rash, pathognomonic of the disorder. Concurrently or in sequence, there is progressive proximal muscle weakness, presenting as fatigue, poor endurance, and gradual impairment of daily activities such as climbing stairs, rising from the floor, or raising the upper extremities.[22,25] Other cutaneous expressions are: telangiectatic papules over the interphalangeal and metacarpophalangeal joints, (Fig 6) elbows, and knees (Gottron's papules); periungual capillary dilation; large poikiloderma plaques on the face, neck, and trunk; livedo reticularis; alopecia; and lipoatrophy.[19,23,26]

The disease evolves, with worsening of the muscle complaints leading even to complete inability to perform movements depending on the limb girdles and proximal muscular groups, speech, and swallowing. Calcifications of subcutaneous tissue develop in approximately two thirds of pediatric patients, and other potential complications are: gastrointestinal vasculitis, myocarditis, restrictive pulmonary disease, and interstitial pulmonary fibrosis; the gradual development of signs of other connective tissue disease occurs in 24% of children.[23,24,26]

Laboratory exams show elevated serum levels of muscle-derived enzymes, mainly creatine phosphokinase, aldolase, lactate dehydrogenase, and aspartate aminotransferase. Around 23% of children with dermatomyositis present positive antinuclear antibodies; myositis-associated antibodies (anti-Mi 2) occur in 20% of cases, and factor VIII–related antigen (von Willebrand factor) increases with endothelial injury.[23,25–27] Magnetic resonance imaging studies are helpful in identifying involved muscles and in selecting better

biopsy or electromyography areas. Accessible indicators to monitor disease activity and detect disease flares are lactate dehydrogenase and aspartate aminotransferase levels.[28]

Before the use of systemic corticosteroids, dermatomyositis was a very serious, commonly fatal disorder. Presently, it is managed with moderate to high dose of corticosteroids, preferably prednisone, 1–2 mg/kg/d, slowly tapered down, according to clinical improvement and decreasing serum enzyme levels. A maintenance dose is often necessary for 1–2 years. Intravenous (IV) pulse therapy with methylprednisolone, 30 mg/kg on alternate days, to a maximum of 1 g/d is also recommended.[29] In cases that do not respond significantly, immunosuppressors could be added. Other approved drugs are IV immunoglobulin, hydroxychloroquine, methotrexate, azathioprine, cyclosporine, extracorporeal photochemotherapy, and others.[1,19] These drugs are options as steroid-sparing agents and in cases of refractory or recurrent disease.

Lupus Erythematosus

Lupus erythematosus is an autoimmune, inflammatory, multisystem disorder of unknown etiology, whose clinical manifestations can be restricted to the skin or involve many organs.

Discoid lupus erythematosus (DLE) is very rare during childhood, comprising <2% of patients.[25,30] Typical skin lesions, similar to those of adults and also without systemic involvement, characterize the disease. Despite the few reported cases, however, important differences are noted when both age groups are compared: lack of female predominance, low incidence of photosensitivity, and more frequent progression to systemic lupus erythematosus.[30]

Dermatological lesions are characterized by erythematous, round (discoid) plaques; individual lesions are sharply demarcated, with adherent scales, follicular plugging, telangiectasia, depigmentation, and atrophic scars. They are most prominent on the face (Fig 7) and scalp and on the light-exposed areas. DLE lesions commonly involve the malar eminence, producing the classic butterfly rash.[22,30]

The diagnosis is confirmed by histopathological exam of skin biopsy; autoantibodies are normally negative and, when positive, represent a good marker to signal evolution to a systemic form of the disease.

Treatment has to be individualized, according to the activity of the disease, and also directed to the prevention of scarring.[22,30] Local steroids are the first choice, eventually under occlusion or by intralesional injection. Hydroxychloroquine is indicated in nonresponsive cases or for those associated with important photosensitivity. In recalcitrant cases, systemic corticosteroids can be associated.[22,24,30]

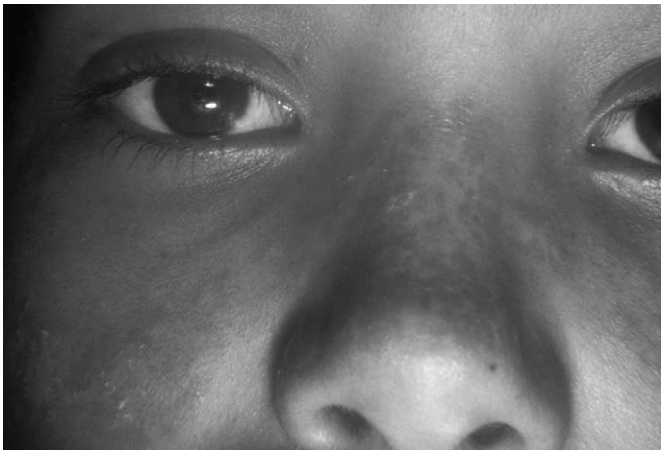

Figure 7. *Discoid lupus erythematosus: erythematous plaques with adherent scales, telangiectasia, depigmentation, and areas of atrophy on the face. (Courtesy of Gabriela Lowy, MD)*

Systemic lupus erythematosus (SLE), in all age groups, is one of the most difficult autoimmune rheumatic diseases to diagnose and manage. It can show a wide spectrum of clinical manifestations, seems to be more severe in children than in adults, and changes over time within an individual patient during different stages of the disease.[31–33]

SLE rarely appears before 4 years of age, the frequency increasing during infancy and adolescence (15–17% of lupus patients), peaking between 20 and 30 years of age. There is a predominance of female patients of 3:1 before puberty, increasing to 7:1 after puberty, and non-Caucasoid individuals are affected more frequently.[1,25,32]

SLE results from the interaction of genetic susceptibility and environmental factors and is characterized by the production of numerous autoantibodies.[24,33] There is evidence that suggest a multigenic genetic susceptibility to SLE, depending on HLA and non-HLA genes. Very young patients usually show complement deficiencies of C2, C4, C1q, and Cr1. Recently, differences for tumor necrosis factor-α, interleukin-10, and Fcγ type IIa and IIIa have been described.[32,34] The disease is characterized by the reactivity and high titers of autoantibodies, mainly anti-DNA. These antibodies are the result of an antigen-specific T-cell–dependent B-cell response.[22,35] Other important autoantibodies are the antiribosomal-P (anti-P) and the antineutrophil cytoplasmic (ANCA). The first one is associated with aggressive SLE, hepatitis, nephritis, and psychosis. It has a high prevalence in children and juvenile SLE; its titers parallel changes in anti-DNA antibodies and are strongly correlated with disease activity.[36] ANCA aids in the diagnosis of systemic vasculitis and is also a marker of the disease activity.[37]

The proposed triggers of the excessive immune response found in SLE could be multiple exposure to

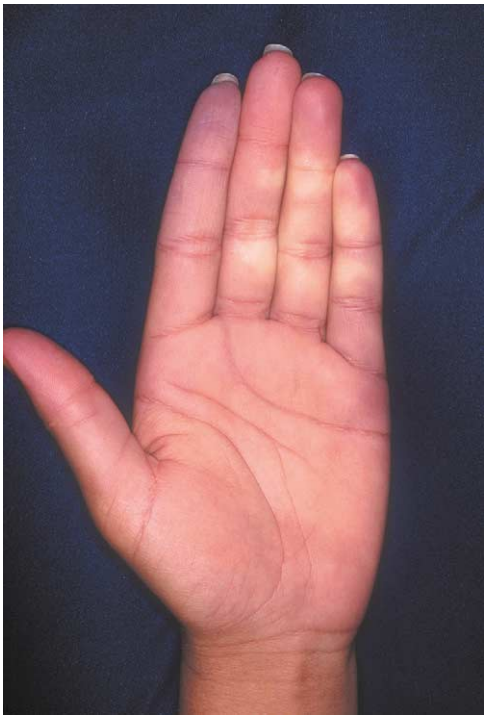

Figure 8. *Systemic lupus erythematosus: Raynaud's phenomenon.*

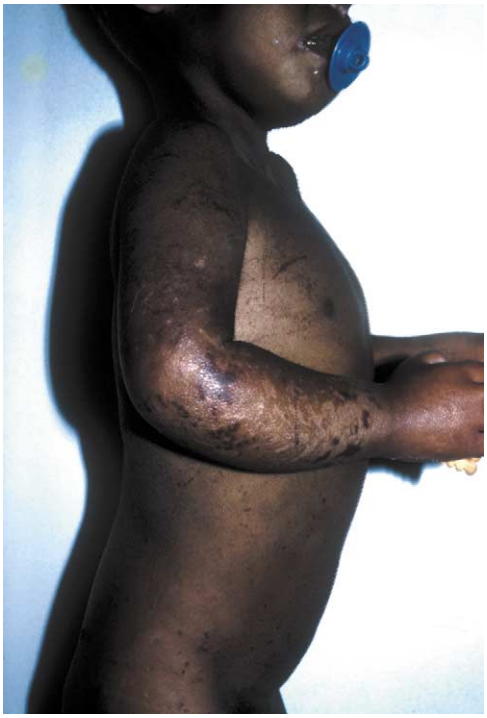

Figure 9. *Kwashiorkor—slightly elevated surface and velvet aspect of the lesions, with a pellagrous aspect. It is usually more visible in dark-skinned individuals. (same patient as in Fig 10)*

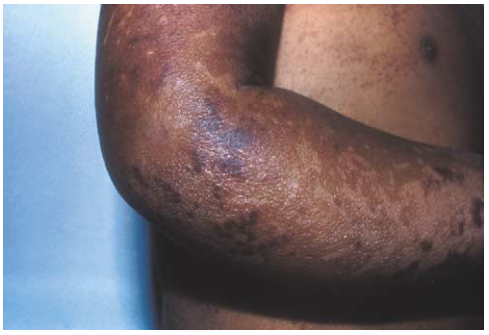

Figure 10. *Kwashiorkor—close view of the affected area. (same patient as in Fig 9)*

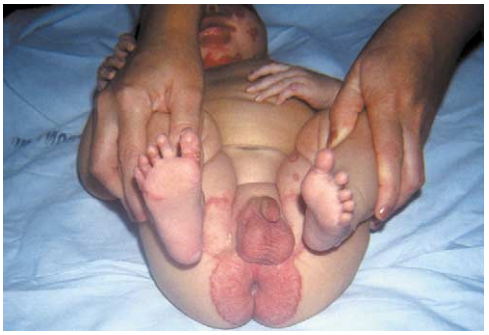

Figure 11. *Acrodermatitis enteropathica—eczematous erosions and desquamation with a psoriasiform aspect, especially on the face and anogenital area. (Courtesy of Gabriela Lowy, MD)*

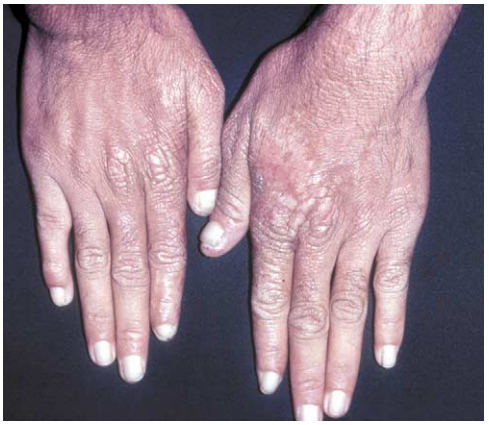

Figure 12. *Lipoido proteinosis: hyperkeratotic, verrucous papules of yellowish-white color, and varioliform scars on the hands. (From the collection of João Ramos-e-Silva, MD)*

exogenous stimuli, including bacteria, viruses, and chemicals, and self–DNA-protein complexes.[35,38,39] The relationship of SLE and sex hormones has been recognized for a long time. Preliminary evidence suggests that women who develop lupus during their reproductive years have a four times greater mortality risk, probably secondary to the influence of estrogens over anti-DNA antibody production.[39,40]

SLE can affect any organ system; however, 80–95% of children with SLE show dermatological lesions. The initial presentation is usually with fever, malaise, weight loss, lymphadenopathy, arthritis, rash, and positive antinuclear antibodies. Other findings include hematological abnormalities such as autoimmune hemolytic anemia, thrombocytopenia and coagulopathies (76–90%); renal compromise, presenting as diffuse nephritis, with high chronicity and poor prognosis (64–80%); cardiac and pulmonary manifestations (5–77%), including pleural effusions, pneumonitis, pulmonary hemorrhage, pulmonary fibrosis, cardiac ischemia, and even acute myocardial infarction involvement; central nervous system symptoms (20–30%), manifested as peripheral neuropathies, cerebrovascular accidents, cerebritis, depression, psychosis, seizures, coma, and myelitis; and musculoskeletal manifestations characterized by painful nonerosive polyarticular arthritis.[1,32,33]

Cutaneous lesions are similar to those of DLE or less specific urticarial or papulosquamous ones, with little scaling, telangiectasia, or scarring. Petechiae, purpuric lesions, nail fold telangiectasia, small digital punctate infarcts, livedo reticularis, and Raynaud's phenomenon (Fig 8), confirming the underlying vasculopathy, have also been described. Mucosal lesions include nasal and palatal enanthemas, eventually with ulcerations; hair loss and scarring or nonscarring alopecia are frequent.[22,24,32]

Corticosteroids are the mainstay for treatment of SLE in children. The starting dose may be 1–2 mg/kg/d, tapered down as soon as good clinical response is achieved.[1] Steroid-sparing drugs are antimalarials, methotrexate, isotretinoin, IV immune globulin, and others. Cyclophosphamide is indicated in patients with severe renal or central nervous system disease. Hydroxychloroquine is very effective in the treatment of cutaneous lesions unresponsive to topical or intralesional steroids and prevents flares of the disease; they are used in doses of 5 mg/kg/d, being safe when accompanied by regular hematological and ophthalmological evaluations.[1,33] Methotrexate is recommended in children for nonrenal SLE, severe cutaneous and articular symptoms, and for those who do not respond to steroids. Administration regimen starts with 2.5–5 mg/wk, slowly increased to 10 mg/wk, while other drugs are removed or according to the clinical outcome.[32] Cyclosporine, tacrolimus, cyclophosphamide, and autologous hematopoietic stem cell transplantation are eventually recommended, with promising results.[33]

Neonatal lupus syndrome (NLS) is a rare condition determined by passive transplacental transfer of maternal anti-Ro(SSA) and/or anti-La(SSB) antibodies during the second trimester. It occurs in approximately 1 of every 12,500 live births and presents a female predominance but no race predilection.[1,33,41]

The most serious clinical involvement of NLS is cardiac, manifested as congenital complete heart block, which approaches 30% mortality depending on gestational age. The cardiomyopathy is detectable as early as 18 weeks of gestation but can eventually present later, after birth.

The other signs of the syndrome are transient, regressing with the decrease and negativity of maternal immunoglobulin G antibodies at around 6 months of age. It includes SLE-like or atrophic skin lesions, mild cytopenia and hepatic abnormalities, and central nervous system vasculopathies.[32,33,42]

Cutaneous manifestations are very similar to those seen in subacute cutaneous lupus erythematosus. Sun exposure, ultraviolet light, or bilirubin lights for the treatment of jaundice initiate the lesions. An erythematous skin rash, with predilection for the scalp and periorbital area, generally occur in the first few days of birth or may be congenital; multiple erythematous, nonscaling, sharply demarcated lesions can also be found on other areas of the body. Skin changes frequently demonstrate the annular polycyclic type of subacute lupus erythematosus, expanding peripherally, leaving a central ecchymotic area. They heal without scars, and transient hyperpigmentation or residual telangiectasia may occur at the sites of previous involvement.[1,22,41]

Management of NLS requires careful monitoring of high-risk mothers, especially those with lupus or Sjögren syndrome with positive circulating anti-Ro/SSA antibodies. Frequent fetal echocardiograms should be performed between 18 and 24 weeks of gestation to detect early fetal bradyarrhythmias or myocarditis. Prenatal therapy with dexamethasone helps in the regression of ascites and effusions but has no effect on the heart block. Plasmapheresis showed variable results. Postnatal therapy requires the use of cardiac pacing in two thirds of infants. Transient cutaneous lesions require no treatment except sun protection. Local and systemic steroids have limited action.[1,24,41]

Kwashiorkor

Kwashiorkor is a form of protein-energy malnutrition in which the caloric intake remains adequate; the protein amount is deficient while carbohydrates are in relative excess.[43] It is more frequent in the impoverished pediatric population, where malnutrition is accountable for inadequate physical development, occur-

ring especially after the first year of life, when breastfeeding is discontinued.[44] Occasionally, similar manifestations can be found in psychiatric patients, as a consequence of bad nutritional habits or in those submitted to surgical procedures that impair adequate food intake.[44–46]

The precise mechanisms responsible for this metabolic disorder are not entirely clear, but it is considered a multiple deficiency syndrome related to lack of essential amino acids, vitamins, and trace elements, particularly zinc.[43,44,46] Etiopathogenetic hypotheses for the clinical manifestations include an excess of free radicals, dietary toxins such as cyanogens and aflatoxins sometimes found in starchy foods, or proinflammatory leukotrienes, which produce edema.[46–50] However, the close resemblance of the advanced skin lesions of kwashiorkor to those of acrodermatitis enteropathica favors the rule of zinc deficiency as an important causal factor, especially considering ulceration, edema, and prompt response to local application of zinc ointment.[44,51]

Symptoms are more prevalent between 6 months and 8 years of age, starting with a gradual failure to thrive, lacking in skeletal and mental development, edema of the extremities, muscle wasting, photophobia, diarrhea, irritability, apathy or humor disturbances, and cutaneous lesions.[43,46,47] Skin findings consist of hypo- or hyperpigmented patches, some of them with a deep purple color, with superficial erosions all over the tegument, with a special predilection for the pressure zones, extremities, and napkin area. The surfaces of the lesions are slightly elevated and depict a velvet character, with a pellagrous aspect, sometimes described as "cracked" or "enamel painted," more visible in dark-skinned individuals (Fig 9 and Fig 10).[44,47] Advanced cases may also show linear fissuring in the flexures, around the ears, in the axilla, in the popliteal and cubital fossae, and between the toes.[44] Mucous involvement is common in chronic forms, with cheilosis, easy bleeding, xerophthalmia, vulvovaginitis, and the presence of chronic candidal infection. Hair becomes dry and sparse; color changes may include a diffuse whitening or a reddish tinge, which are very characteristic.[44,52] The so-called "flag sign" corresponds to bands of dark and light colors that represent the periods of worsening in the nutritional condition. Nails are brittle, thin, and soft, being easily separated from the nail bed. Patients generally maintain their subcutaneous fat, and the associated edema contributes to the chubby appearance, wrongly taken as a "healthy" aspect.

Complications of kwashiorkor depend on the severity of the disease. It comprises persistent edema secondary to hypoalbuminemia, hypoglycemia, hypothermia, coma, and bacterial or parasitic infections.[43] Differential diagnosis includes acrodermatitis enteropathica, marasmus, pellagra, and inborn metabolism errors.

Treatment of kwashiorkor is directed to replace proteins, and complete recovery is usually achieved with adequate diet correction.[47] Besides, it is necessary to rule out and treat associated diseases, such as malabsorption, infections, gastrointestinal parasitoses, immune deficiency, and even cystic fibrosis.[53] There is a high mortality rate in severe or relapsing case, and neurological and development impairment is seldom fully recovered.

Acrodermatitis Enteropathica

Acrodermatitis enteropathica is a rare disease caused by alteration of zinc metabolism, either hereditary by autosomal recessive transmission, or acquired. This article discusses the hereditary form that occurs in children. Usually fatal when not treated, it presents a universal distribution without preference of race or sex and, due to greater interest in Europe, the majority of cases have been reported from that continent.[54,55]

Clinical manifestations generally begin in babies 4–6 weeks old, after weaning, or even earlier in the absence of breastfeeding, with occurrence of acral dermatitis, eczematous and desquamative pustular lesions (psoriasiform), and erosions on the face, scalp, and anogenital region (Fig 11). Perlèche is a common precocious manifestation, which may also indicate a relapse of the clinical condition.[56] Hands and feet are rapidly affected, presenting paronychia, dermatitis in fingers and palms, and accompanied by annular lesions with a desquamative collar. In healthy areas of the skin, together with the more typical manifestations, vesicobullous lesions may occur.[57] Hair loss from postnatal telogenous effluvium gradually worsens.

Diarrhea, the most frequent gastrointestinal symptom, may or may not be present[58] and, if severe and persistent, leads to a worsening of the clinical course with hydrolytic disturbance. As zinc interacts with copper, the plasmatic levels of this oligoelement can also be reduced, occurring in such cases a hemolytic anemia, refractory to treatment with an iron supplement. Neutropenia and hyperceruloplasminemia may be present.[54,58] The zinc deficiency also damages the immune response, and secondary recurrent infections by bacteria or *Candida albicans* are aggravating factors of the disease.

With evolution of the clinical condition, other manifestations become evident as the child reaches adolescence; with highlight for hypogonadism in boys, growth retardation, and mental and emotional disturbances. Photophobia develops gradually and seems to occur entailed by a zinc-dependent retinal protein.[54]

The specific cause of the genetic anomaly of zinc metabolism is still unknown. Absorption of this element is made in the proximal small intestine in about 2–3% of patients, while the normal absorption ranges

from 27–65%. Once absorbed, 60% of the zinc circulates in the blood associated with albumin and 40% with other proteins. Breast milk is very effective to prevent progress of the disease, and, despite having a lower zinc content than cow's milk, breast milk contains zinc-binding substances, with the most important being picolinic acid. In cow's milk, zinc is associated with casei, avoiding its absorption.[58] The nature and existence of these substances are still controversial.[59] Besides alteration of the intestinal mucosa, it was found that an isolated human fibroblast from a patient with enteropathic acrodermatitis showed significantly reduced zinc transport when compared with normal fibroblasts. It is possible that a zinc-transporting protein or one associated with its transportation is involved. Thus, one of the hypotheses for pathogenesis of enteropathic acrodermatitis is that the genetic alteration found in patients would affect the expression of that protein,[60] and, therefore, breastfeeding would retard the appearance of the disease.[58]

Diagnosis is clinical and should be confirmed by the reduced plasmatic zinc content. Alkaline phosphatase is also generally reduced, and determination of zinc levels in urine and hair is another means that may be used.[54,58] Diagnoses of epidermolysis bullosa, in its several forms, mucocutaneous candidiasis, celiac disease, nutritional deficiencies, and deficiencies of amino acids must be excluded.[58]

Treatment of enteropathic acrodermatitis includes basically a dietary or IV supplementation of pentahydrate zinc sulfate, in a 30–50 mg dose, twice or three times a day. Clinical response is very rapid, with reversal of the clinical condition in days or weeks, depending on the degree of depletion. Mental disturbances generally disappear in 24–48 hours, and the skin begins to recover in 5–7 days, as well as diarrhea, in a gradual way. Precocious replenishing of zinc also restores cellular immunity of these patients, and alopecia is the last alteration to improve.[58,61–63]

The prognosis is good if the treatment is begun early. These patients must receive a zinc supplement during their entire life, with a minimum dose required to prevent relapse. It is very important to observe the toxicity of an overdose; thus, patients who receive this supplementation must be monitored by periodic blood cell count, evaluation of alkaline phosphatase, investigation for blood in stool, and the dosage of zinc and copper in serum.[54,58]

Lipoid Proteinosis

Lipoid proteinosis, hyalinosis cutis et mucosae, or Urbach-Wiethe disease is an uncommon and severe hereditary, autosomal, and recessive metabolic illness, which can evolve fatally. Affected children present hoarseness since birth and, gradually, persistent noninflammatory papules appear on the skin and mucous membranes, associated with a hardened and diffuse edema.[64]

The illness was described in 1929 by E. Urbach and C. Wiethe, respectively a dermatologist and otorhinolaryngologist, who called it *lipoidosis cutis et mucosae,* owing to the histological demonstration of a material associated to protein. This name was later changed to lipoid proteinosis.[65]

The primary defect of this disease seems to be caused by a lysosome alteration, whose biochemical nature is yet to be established. There is a diffuse deposit of hyaline basement membrane–like material in the connective tissue of mucosae, skin, respiratory and upper digestive tract, central nervous system, and other tissues. This material contains an excess of glycoprotein matrix and a smaller amount of collagen fibers. Some authors think that the disease cannot be considered a genetic defect only of collagen, but also resulting from alterations of fibroblast cell activity, epithelium, and endothelium, with reduced production of fibrous collagen and overproduction of basement membrane collagen.[64,66] Costagliota and colleagues[67] demonstrated that a defect in glycoprotein synthesis, possibly enzymatic, could be the cause of lipoid proteinosis and its clinical manifestations. Consanguinity of affected parents and siblings, besides the equal number of men and women affected, suggests autosomal, recessive transmission.[64]

The first and most frequent clinical sign is hoarseness caused by infiltration of laryngeal mucosa, which develops at birth and during childhood. Cutaneous lesions can occur at the same time or after those of the mucosa. These manifestations are sometimes precipitated by vaccination or other illnesses of benign nature. Nodules, hyperkeratotic verrucous plaques of yellowish-white, and varioliform scars and crusts occur more frequently on the face, neck, hands (Fig 12), and knees, possibly due to frequent trauma in those regions. Eyelids may present numerous papulae along their free border. Face lesions appear similar to solar elastosis, and those of the scalp lead to alopecia. The yellow color of the otherwise-pale lips is characteristic.[65,68]

There were reports describing lesions in the scrotum, penis, back of feet and axillae, infiltrations in the tongue, buccal mucosa, frenulum, and palate, leading to limited mobility.[69] Involvement of other organs includes recurrent parotitis; alterations in the respiratory and upper digestive tract with subsequent obstruction; and damage to the nervous system with epileptic crises of the type "déjà vécu," psychosis, intercranial parasellar calcifications, strokes, and eye damage, with ulceration of the cornea. Cardiac, endocrinal, and urogenital alterations have been seen, but whether they are part of the disease spectrum remains unclear.[65,66]

Laboratory exams are not typical for lipoid proteinosis. In some patients, the abnormal glycose metabolism

and/or alteration of protein electrophoresis has been reported. Porphyrins and liver function must be assessed.[65] In the histopathology of cutaneous lesions, periodic acid-Schiff positive hyaline material is observed in the dermis, around capillaries, and sudoriparous glands.[69] There is a report on a case of diffuse distribution of type IV collagen in the connective tissue of an oral mucosa lesion observed by immunohistochemistry.[70]

The main differential diagnosis must be made with erythropoietic protoporphyria; however, lesions are restricted to sun-exposed areas in this disease, as well as only the superficial dermis presents alteration. Presence of hoarseness in lipoid proteinosis also helps in the distinction of both diagnoses.[64]

There is no effective therapy; however, topical corticoid therapy has been used with average results. Dimethyl sulfoxide has controversial effectiveness,[65] and surgical excision, which consists in the removal of the lesions, is sometimes necessary with a functional purpose for straightening of the laryngeal lumen.[71]

Phenylketonuria

Phenylketonuria is a rare, hereditary, autosomal, and recessive disease, with an approximate frequency of 1:100,000 births. It is caused by deficiency of the phenylalanine hydroxylase enzyme or its cofactors.[72,73] The alteration is due to genetic mutation, resulting in an innate error in the metabolism of L-phenylalanine, resulting in its high concentration in blood.[73] The resulting hyperphenylalaninemia is associated with mental retardation; convulsions; hypopigmentation of skin, hair, and eyes; and eczematous dermatitis. Hypopigmentation seems to be caused by the association of phenylalanine at sites of tyrosinase-hindering oxidation of tyrosine to melanin.[72,74]

Newborns presenting phenylketonuria have blond hair, blue eyes, and hypopigmented skin. Eczematoid and sometimes scleroderma-like lesions are frequent,[72] and it is believed that the increase of manifestations of atopic dermatitis[75,76] is due to the existent vasoconstriction.[77] There is a low occurrence of pigmented nevi, when compared with family members, and a frequent presence of keratosis pilaris. Mental retardation, athetosis, unrest, increased tendon and muscular tonus reflexes, hyperkinesis, and convulsions accompany the disease if it remains untreated.[72] A study performed in China with 228 patients with phenylketonuria showed mental retardation in 94.5% and development of epilepsy in 48.9% of them.[78]

Diagnosis is confirmed by detection of higher levels of phenylalanine metabolites in urine through the $FeCl_3$ test, which renders an olive-green color to urine in the presence of phenylpyruvic acid. Dosage of phenylalanine in serum can also close the diagnosis. In the differential diagnosis, albinism and Chediak-Higashi syndrome must be excluded.[72]

A diet without phenylalanine leads to improvement of symptoms, and recent investigations demonstrated normalization of L-phenylalanine concentration with oral administration of a natural cofactor of the phenylalanine hydroxylase enzyme, (*6R*)-L-erythro-5,6,7,8-tetrahydrobiopterin.[72,73,79] Restriction should be applied very carefully because neurological damage can be irreversible. In this sense, immediate application of the postnatal foot test in babies is extremely important.

Table 1. Cutaneous manifestations in diabetes mellitus

Cutaneous diseases associated primarily with diabetes mellitus
Limited joint mobility syndrome*
Diabetic dermatopathy*
Necrobiosis lipoidica diabeticorum*
Disseminated granuloma anulare
Bullous diabeticorum
Buschke's scleredema
Kyrle's disease
Cutaneous diseases secondary to complications from diabetes mellitus
Eruptive xanthoma*
Lipoatrophy/lipohypertrophy in sites of insulin injections*
Infections*
Candidiasis*
Severe and recurrent staphylococcal infections*
Malignant otitis externa (*Pseudomonas*)
Skin manifestations associated with diabetes mellitus
Vitiligo*
Acanthosis nigricans*
Hemochromatosis*
Lipodystrophy*

* *Observed in childhood.*

From Lucky AW. Cutaneous manifestations of endocrine, metabolic, and nutritional disorders. In: Schachner LA, Hansen RC. Eds. Pediatric Dermatology. 2nd ed. New York: Churchill Livingstone, 1995:1043–85.

Cutaneous Manifestations in Diabetes Mellitus

Diabetes mellitus is a common disease with cutaneous manifestations present in 82% of the patients.[80] Skin lesions may be primary to the process of the disease, entailed from its metabolic alterations; secondary to the diabetic state, such as caused from macro- and microvascular damage; secondary to infection; or also manifestations from associated diseases (Table 1).[81–83]

There is a distinct familial predisposition to develop type I diabetes with preponderance of certain HLAs (HLAB8, HLABW15, HLADW3, and HLADW4). Prevalence rate is 0.9:1000 in schoolchildren. Some cutaneous manifestations, notably necrobiosis lipoidica, can precede type II diabetes mellitus.[82]

Cutaneous Diseases Associated Primarily With Diabetes Mellitus

Limited joint mobility syndrome is a diffuse process causing contraction of hand joints, leading to incapacity

to extend fingers fully. A thickening of the skin occurs with keratosis, mainly on the back of the hands, and expansion of joints. Thirty percent of the cases occur in the first 20 years in patients with type I diabetes, and the histopathology of the affected regions shows an increase of dermic collagen.[82]

Diabetic dermatopathy is characterized by pretibial pigmented maculae, occurring in 50% of diabetic adults and very rarely in children. The lesions start with small papulae that evolve into brownish-red and later yellowish maculae, which may be depressed. Histopathologically, it is similar to progressive pigmentary purpura with extravasation of red blood cells, hemosiderin, and light lymphohistiocytic infiltrate.[82]

The lesions of necrobiosis lipoidica diabeticorum appear characteristically in the frontal tibial region but can also occur in the arms and trunk[83] and are present in about 0.3% of the patients with diabetes. Lesions may vary in number, from few to many, unilateral or bilateral. The initially small nodules, dark red, slowly expand, changing to irregular, flat, and depressed plaques when the skin becomes atrophic. The color turns brownish-yellow, except at the border, which remains reddish. Delicate blood vessels are visible through surface transparency caused by the prominent atrophy.[84] There is a tendency to ulceration with slow resolution. Lesions are generally asymptomatic but sometimes can be anesthetic due to destruction of cutaneous nerves.[85] Necrobiosis lipoidica has a strong association with the disease and may be considered as one of its manifestations or even as a predecessor of diabetes mellitus type II.[82,83] From the histological standpoint, there is necrobiosis of the collagen and infiltration of histiocytes in palisade and accumulation of mucin.

High-potency occlusive and intralesional corticoids have been used with little success, and in some cases, skin grafts can improve cosmetic appearance. Aspirin and dipyridamole, despite being referred to as therapeutic options, are ineffective.[82]

Secondary Cutaneous Diseases and Metabolic Alterations in Diabetes Mellitus

In uncontrolled diabetes type I, intense hypertriglyceridemia may occur and diffuse xanthomatosis or eruptive xanthoma may develop. The lesions consist of firm, yellowish papulae that may coalesce and disappear by controlling hypertriglyceridemia. Lipodystrophies may be lipoatrophy or hypertrophy and occur in spots of insulin injection in 15–55% of the patients. The symptoms may resemble urticaria and are rarely anaphylactic, and some cases may be treated with desensitization.

It is unknown whether the cutaneous lesions of infections associated with diabetes mellitus are more frequent or simply more severe in diabetic patients. Candidiasis occurs in many locations, as oral mucosa (perlèche), vaginal mucosa (vaginitis), nails (onychomycosis), ungual folds (paronychia), and intertriginous areas (intertrigo). Topical antifungal drugs are usually effective. Recurrent *Staphylococcus* infection, as furunculosis, is common in diabetics, with some patients presenting *Staphylococcus* inside the nose, thus acting as carriers. Mucormycosis of the nasal cavity may cause perforation in ill-controlled diabetes patients. Reports of destructive infections in children are rare.[82]

Other Diseases Associated With Diabetes Mellitus

Vitiligo occurs with greater incidence (4.8%) in patients with diabetes mellitus non-insulin-dependent, and can precede the beginning of clinically evident diabetes.[84] It is believed that there is an autoimmune base in its pathogenesis, and it may also occur in patients with thyroid and adrenal illness. Hemochromatosis is a disease resulting from excessive accumulation of iron that can destroy pancreatic cells, causing bronze diabetes. These patients have deep and diffuse hyperpigmentation caused not only by the deposit of iron in the skin but also from hypermelanization.[82] Acanthosis nigricans is characterized by velvetized papillomatous hyperplasia of the epidermis with intense pigmentation, more prominent in axillae, inguinal and inframammary region, and neck. It is suggested that the pathogenic mechanism of acanthosis nigricans is connected to endocrinopathies. Studies in patients with a series of endocrine diseases and acanthosis nigricans suggest that resistance to insulin is a common factor during absence of a clear diabetic condition.[84]

Cutaneous Manifestations in Thyropathies

Thyroid hormones act in the fundamental metabolic mechanism, in the biosynthesis process, and in cellular degradation. They appear to have several primary action locations, such as cell membranes and mitochondria; gene transcription, which increases and makes the substrate and oxidation mechanism available, and regulate functional properties, including those of the keratinocytes and fibroblasts.[86,87]

Hypothyroidism, caused by absence or reduction of the thyroid hormone, may be congenital or acquired, associated with an increase (goitrous hypothyroidism) or atrophy or absence of the gland (nongoitrous hypothyroidism). It is rarely caused by pituitary malfunction or insensibility of the target organ to thyroid hormones.

In its congenital form, it affects 1:4000 newborns, affects equally both sexes, and is the greatest cause of mental retardation. In its secondary form, by congenital pituitary malfunction, it is even more rare, occurring in 1:68,200 newborns later during childhood with frequent association to Hashimoto's thyroiditis. It has a preference for the female sex and positive family history regarding thyropathies and other autoimmune diseases.[82,88]

There are few clinical symptoms at birth; the children tend to be docile with cold, xerotic, and vasoconstricted skin and frequently presenting cutis marmorata. They may present a condition called myxedema, characterized by a yellowish skin, resulting from a combination of anemia, icterus, and carotenemia, attributed to the hepatic defect in conversion of beta-carotene into vitamin A, besides infiltration of mucopolysaccharide acids, hyaluronic acid, and chondroitin sulfate. These deposits are more prominent around the eyes and on the lips and tongue, causing macroglossia. They may also occur as focal mucinosis with small papules.[89] Sometimes follicular plugging with thin and hyperkeratotic epidermis is observed.[90]

Hair is dry, thick, fragile, and slow-growing; there is diffuse loss of scalp hair and distal third of the eyebrows, as well as a reduction of body hairs. Nails are fragile and slow-growing. Patients with hypothyroidism, especially children, often develop lanugo type of hair on back, shoulders, and extremities.[90,91,92] There are also distinct reports of collodium baby and chronic mucocutaneous candidiasis associated with congenital hypothyroidism.[93,94]

The development of the brain and normal child growth are dependent on the normal thyroid hormone levels.[82,88] In about 20% of infancy forms of vitiligo, there is an association with subclinical thyroiditis or with an increase of autoantibodies against the gland; variations of these titers are similar to anti-melanin antibodies.

Diagnosis of primary hypothyroidism is based on low levels of thyroxine (T4) with high levels of circulating thyroid-stimulating hormone. In secondary hypothyroidism due to malfunction of the pituitary gland, there is depression of T4 together with normal or low levels of thyroid-stimulating hormone. For its treatment, it is necessary to replenish the thyroid hormone adequately, preferably with synthetic L-thyroxine. Newborns with severe hypothyroidism should be hospitalized, and, if the treatment is started precociously, profound mental retardation is prevented. Replenishing should be done slowly to avert cardiovascular malfunction.[82]

Hyperthyroidism, or its more advanced stage, thyrotoxicosis, is normally caused by an autoimmune thyroid disease or by chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) or Grave's disease.[82]

Grave's disease is the most common cause of hyperthyroidism in children. It may occur at any age, including newborns, and increases in frequency as adolescence approaches. Girls are five times more affected. Opthalmopathy occurs but is not as severe as in adults. One of the first symptoms of the disease is extreme unrest and lack of attention, leading to difficulties in school.[88]

An increase of the thyroid gland (goiter) is present in almost all cases. Signs and symptoms include high blood pressure, irritation, exophthalmos, frontal bossing, and microcephalia, among others. Cutaneous symptoms of thyrotoxicosis include heat; intense sweating, mainly in hands and feet; face flush; and a very smooth and velvetlike skin. The heat is caused by peripheral vasodilatation and increase of blood flow, which also causes the persistent face flush, elbow redness, and hand erythema.[90] Patients may complain about generalized itching. Diffuse hyper pigmentation of unknown etiology and alopecia areata may be present.

In Grave's disease, there are three specific symptoms: opthalmopathy, pretibial myxedema, and thyroid acropathy.[82] Pretibial myxedema lesions are pink nodules with well-defined borders, shiny, and bilateral but not symmetric, usually in the front of the tibia. They occur due to accumulation of mucopolysaccharides, mainly hyalonuric acid. Although rare in small children, it occurs in adolescents.[90] Hair characteristically becomes thin, fragile, and oily. Nails present onycholysis, especially the fourth finger (Plummer's nail).

High levels of free T4 confirm laboratory diagnosis, and the thyrotoxicosis secondary to Grave's disease usually responds to antithyroidal drugs as methimazole and propiltiuracil, whose most adverse effect is agranulocytosis. Although thyrotoxicosis may be controlled by medication, surgery is considered the treatment of choice with certain frequency due to problems from the long period of using those drugs. There is no specific efficient therapy for treatment of pretibial myxedema, but systemic and intralesional corticoids have shown a certain efficacy.[82]

Cutaneous Manifestations in Adrenal Diseases

The adrenal cortex produces three large groups of hormones: glucocorticoids, mineralocorticoids, and androgens. Biosynthesis of steroid hormones by the adrenals is controlled by the hypophysis through adrenocorticotropic hormone (ACTH), which in turn is controlled by the hormone that releases corticotrophin from the hypothalamus. An excess or deficiency of glycocorticoids and androgens can cause several types of cutaneous manifestations.

Adrenocortical insufficiency can occur in the presence of atrophy of the suprarenal glands. This may be idiopathic, entailed by a destructive illness (e.g., tuberculosis), by surgical ablation, by inadequate stimulation by ACTH, or when glycocorticoids synthesis is insufficient due to an abnormal biosynthesis (e.g., adrenogenital syndrome). With the exception of adrenogenital syndrome, the other causes also lead to a loss of androgens.[82,90]

Adrenocortical insufficiency, also known as hypoadrenalism or Addison's disease, is rare but occurs also

in children and adolescents, and both sexes are equally affected. The primary form appears in family groups that may present other manifestations of autoimmune endocrinopathies, such as hypoparathyroidism, pernicious anemia, and vitiligo. Congenital adrenal hypoplasia seems to occur in approximately 1:12,500 births.[82,90,95]

Unless the patient is severely weakened, skin texture seems normal, and the most remarkable skin alteration from chronic adrenal insufficiency is the almost uniform pigmentation. This is the first manifestation of the disease in 20–40% of the cases, and this hyperpigmentation, resulting from excessive ACTH, is the main differential between adrenal insufficiency due to pituitary malfunction and primary adrenal failure.[90,95] Darkening of the areola, scrotal region, lips, preexistent nevi, hand and foot wrinkles, and scars are prominent. Pigmentation of the linea alba may appear on the lower abdomen, as well as a longitudinal pigmented line in nails. In postpubescent patients, pubic and axillary hair becomes scarce, and some patients complain about hair loss. In the mucosae, bluish-black pigment deposition may be seen in the gingivae along its borders and also in the hard palate. The overall appearance of the patient is pale and tired.[82]

Reduction or absence of cortisol can be diagnosed by dosing the levels of 17-hydroxysteroids in the plasma and in the 24-hour urine or, if available, by measuring the urinary free cortisol. However, the best diagnostic test for adrenal insufficiency is checking the lack of increase in 17-hydroxysteroid levels in response to intramuscular or endovenous stimulation by ACTH. Metabolic abnormalities include decrease of sodium and rise of potassium, with hyperglycemia. Pituitary hypothalamic insufficiency of ACTH may be diagnosed by adrenal failure in the production of 11-deoxycortisol during the metyrapone test. Such patients maintain the normal mineral corticoid function and do not present pigment abnormalities. By replenishing the glycocorticoids levels, a quick reversion of symptoms is obtained, including hyperpigmentation.[82]

Hyperadrenalism can occur due to functional tumors of the adrenal cortex (Cushing's syndrome), from adrenal hyperplasia due to inadequate secretion of ACTH by the pituitary gland (Cushing's disease), or from nonpituitary neoplasia (ectopic ACTH syndrome).[90]

The term Cushing's syndrome is applied to the excessive production of glycocorticoids, specifically cortisol, as a response to hormonal stimuli from the pituitary and/or hypothalamus. All these causes, except the one due to exogenous administration of steroid hormone, can be manifested by associated signs of androgen and glycocorticoid excess. Congenital adrenal hyperplasia is expressed by low glycocorticoid production due to an enzymatic defect specifically in cortisol biosynthesis and resulting in increased production of androgens.[82]

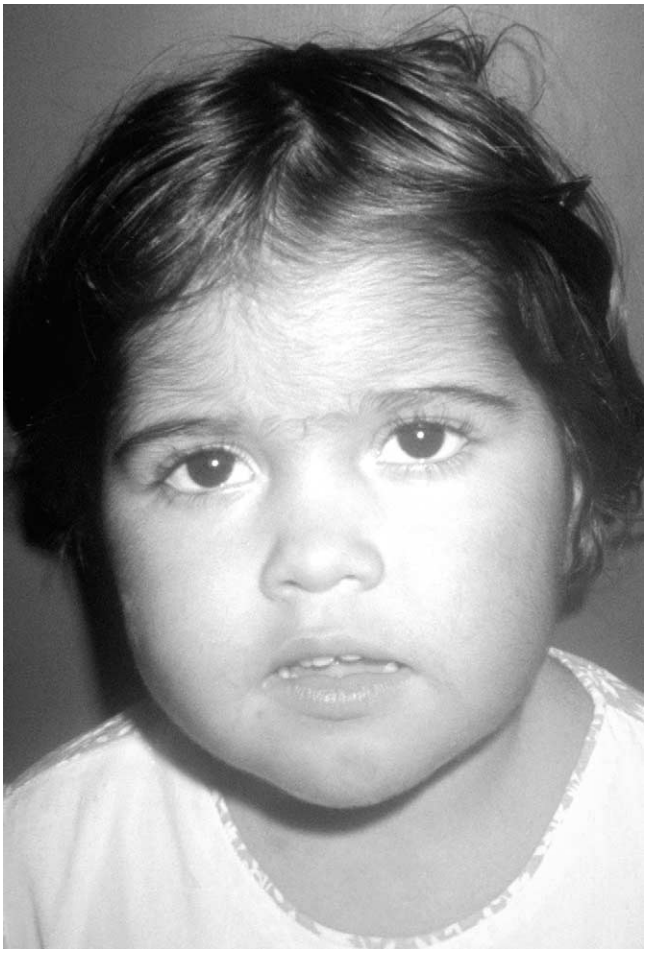

Figure 13. *Cushing's syndrome and hirsutism due to iatrogenic cause—exogenous administration of systemic high-potency steroids. (Courtesy of Gabriela Lowy, MD)*

Cushing's syndrome and adrenal tumors, despite being rare in children and adolescents, can occur at any age. The excess of cortisol in younger children is normally caused by adrenal tumors. After 6 or 7 years of age, Cushing's syndrome is more frequent; however, the most common cause is iatrogenic (exogenous administration of systemic or topical high-potency steroids) (Fig 13 and Fig 14).

The skin usually becomes atrophic, with a thin and shiny appearance, possibly with light desquamation. It is friable and easily hurt. These patients are prone to dermatophytosis and pityriasis versicolor. They also present capillary fragility and frequently develop petechiae and ecchymoses after minimal trauma. Among the characteristic lesions from excess glycocorticoids are wide purple striae that appear in regions subject to tension. The presence of hyperpigmentation and acanthosis nigricans may occur, but it is normally discrete. Plethora is common, accompanied by facial telangiectasia, as well as hypertrichosis and acne. There is a redistribution of subcutaneous fat, and its accumulation

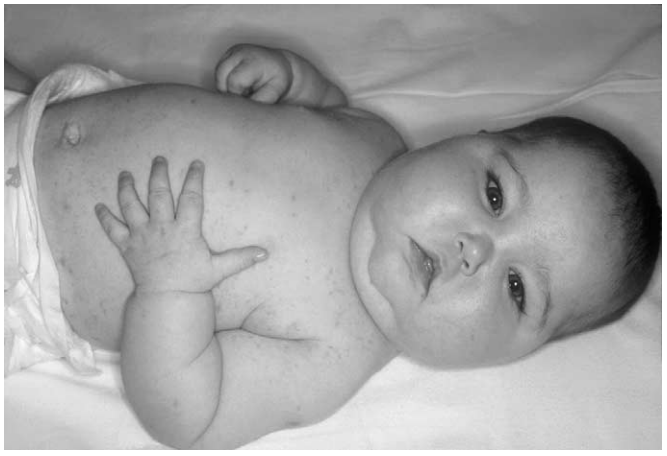

Figure 14. *Cushing's syndrome caused by systemic steroids.*

causes a "full moon face" in cheeks and "buffalo gibbus" in the upper thoracic region. Perifollicular pustules, all in the same evolutionary stage, appear on the back, upper limbs, thorax, and face. Candidiasis occurs in oral and vaginal mucosae and other locations. Infections caused by bacteria, especially *Staphylococcus*, may cause diffuse folliculitis, furunculosis, and abscesses.[82,90]

Excessive glycocorticoids are verified by free cortisol dosage in the 24-hour urine and by plasmatic cortisol levels, showing absence of the normal daily variation. Cortisol in the plasma is higher in the morning and lower in the afternoon. Tests such as dexamethasone suppression, and imaging diagnosis, such as ultrasound and CT, help to differentiate the excess pituitary ACTH from a primary adrenal tumor.[82]

Cushing's syndrome has been treated with bilateral adrenalectomy, followed by replenishing of glycocorticoids and mineralocorticoids.[96]

Excessive production of androgen leads to virilization in adult women and to precocious puberty when present in preadolescents. The excess of circulating androgens can contribute to development of certain skin lesions, including acne, hirsutism, and alopecia. The causes for excess of androgens are various, among them tumors, as well as overproduction of androgens in the ovary and/or adrenals and exogenous use of anabolic steroids by athletes.

In the virilization syndrome, the skin becomes thicker; face pores remain open with excessive oil production, and acne may develop. Hair configuration in the child becomes similar to that of an adult (frontal baldness in adolescents), and androgenetic alopecia may be present. Hair growth is accelerated, and the hair threads are thicker in upper and lower limbs, upper thorax, and beard area. Pubic and axillary hairs are more developed in children; the genitals show masculinization; with increase of the clitoris in women; and penial hypertrophy, with increase of skin folds of the scrotal pouch in prepubertal men. When this virilization occurs during fetal life in women, it may cause pseudo-hermaphroditism. Hyperpigmentation of the perineum, external genitalia, axillae, and nipple are present. The adrenogenital syndrome is one of the main causes of virilization.[82,90]

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