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CUTANEOUS MANIFESTATIONS OF ENDOCRINE DISEASES IN CHILDREN

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Endocrine diseases such as obesity, diabetes mellitus, Cushing's syndrome, hypothyroidism and hyperthyroidism, acromegaly and hyperandrogenism in children and adolescents are often manifested by changes in the skin. Moreover, skin symptoms can be a marker of systemic, in this case, endocrine and metabolic diseases. Obesity and diabetes are chronic diseases that affect people all over the world, and their incidence is increasing in both children and adults. Clinically, they affect a number of organs, including the skin. The cutaneous manifestations caused or aggravated by obesity and diabetes are varied and usually bear some relation to the time that has elapsed since the onset of the disease. They include acrochordons, acanthosis nigricans, striae, xerosis, keratosis pilaris, plantar hyperkeratosis, fungal and bacterial skin infections, granuloma annulare, necrobiosis lipoidica. In obese patients, psoriasis and atopic dermatitis are more common than in the control group. With the pathology of the thyroid gland, diseases such as alopecia, pretibial myxedema, urticaria, and some others develop. Hyperandrogenism (polycystic ovary syndrome) is accompanied by skin lesions such as acne vulgaris, hirsutism, androgenic alopecia, acanthosis nigricans. This literature review focuses on the main skin syndromes accompanying endocrine pathology in children and adolescents. Information about such clinical associations can make it easier for pediatricians and endocrinologists to diagnose and treat endocrine diseases in a timely manner and, thereby, prevent long-term adverse consequences.

Keywords: obesity; diabetes mellitus; hypothyroidism; hyperthyroidism; Cushing's syndrome; hirsutism; skin manifestations.

ПОРАЖЕНИЕ КОЖИ ПРИ ЭНДОКРИННЫХ ЗАБОЛЕВАНИЯХ У ДЕТЕЙ

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Эндокринные заболевания, такие как ожирение, сахарный диабет, синдром Кушинга, гипотиреоз и гипертиреоз, акромегалия и гиперандрогения, у детей и подростков нередко проявляются и изменениями со стороны кожи. Более того, кожные симптомы могут быть маркером системных, в данном случае эндокринных и метаболических, болезней. Ожирение и диабет — это хронические заболевания, которые распространены по всему миру и поражают несколько органов, включая кожу. Хотя оба заболевания чаще встречаются у взрослых, их распространенность среди детей возрастает. По данным Всемирной организации здравоохранения, 20 % детей и подростков в Европе имеют избыточный вес, а треть из них страдают ожирением. Кожные проявления, вызванные или усугубляемые ожирением и диабетом, разнообразны и обычно имеют некоторую связь со временем, прошедшим с начала заболевания. К дерматозам, ассоциированным с сахарным диабетом и ожирением, относятся мягкие фибромы, черный акантоз, стрии, ксероз, фолликулярный гиперкератоз, подошвенный гиперкератоз, грибковые и бактериальные инфекции кожи, кольцевидная гранулема, липоидный некробиоз. У больных ожирением чаще, чем в контрольной группе, встречается псориаз и атопический дерматит. При патологии щитовидной железы развиваются такие заболевания, как алопеция, претибиальная микседема, крапивница и некоторые другие. Гиперандрогения (синдром поликистозных яичников) сопровождается такими поражениями кожи, как вульгарные угри, гирсутизм, андрогенная алопеция, черный акантоз (acanthosis nigricans). Этот литературный обзор посвящен основным кожным синдромам,

сопровождающим эндокринную патологию у детей и подростков. Информация о подобных клинических ассоциациях может облегчить педиатрам и эндокринологам своевременную диагностику и лечение при эндокринных заболеваниях и тем самым предотвратить отдаленные неблагоприятные последствия.

Ключевые слова: ожирение; сахарный диабет; гипотиреоз; гипертиреоз; синдром Кушинга; гирсутизм; кожные проявления.

INTRODUCTION

Dermatologists often observe various skin changes that are characteristic of certain endocrine diseases. The identification of endocrinopathy is very important because patients will be able to receive pathogenetic rather than symptomatic treatment. Metabolism and endocrine gland disorders accompanied by skin lesions include obesity, diabetes mellitus (DM), hyperthyroidism, hypothyroidism, Cushing syndrome, acromegaly, and hyperandrogenism.

Cutaneous manifestations of DM and obesity are directly related to the onset age and duration and severity of the underlying disease.

Diabetes mellitus

DM represents a heterogeneous group of disorders characterized by high blood sugar levels and impaired lipid and carbohydrate metabolism. DM is classified according to pathogenesis as type 1 (T1DM) or type 2 (T2DM), and each type has particular clinical characteristics. Complications associated with DM are multifactorial in origin and result from biochemical, structural, and functional disorders. Approximately 30% of adult patients with DM will have cutaneous manifestations at some point in their lives; the timing varies depending on the DM type, patient's age, and disease duration. Children are not exempted. In the pediatric population, T1DM occurs predominantly with an average onset age of 8 years. Owing to the increasing prevalence of obesity and insulin resistance, the detection rate of T2DM has also increased, mainly in children aged >10 years [6, 7, 10, 26].

In 1985, a classification was proposed that distinguishes between skin diseases caused by DM, associated with DM or insulin therapy, and skin manifestations of insulin resistance [10] (Table 1).

Skin changes caused by DM. High blood glucose levels and damage to the vascular and nerve structures characteristic of DM cause skin changes and diseases such as xerosis, follicular hyperkeratosis, rubeosis, infections, limited joint mobility, microangiopathy, and neuropathy.

Xerosis, or dry skin, is one of the earliest and most common symptoms of DM and occurs in 22% of patients with type 1 DM [6, 44]. Interestingly, even in the absence of clinically evident xerosis, the skin of patients with DM exhibits abnormal desquamation and decreased elasticity, as well as an increase in thickness, which may contribute to a decrease in its elasticity.

Skin thickening is clinically divided into three categories, namely benign skin thickening, scleroderma-like syndrome, and Buschke scleredema. Thickening of the skin in DM is considered caused

Table / Таблица

Cutaneous manifestations in children with diabetes
Кожные проявления у детей с диабетом

Skin changes caused by diabetes / Изменения кожи, вызванные диабетом	Skin conditions associated with diabetes / Кожные заболевания, связанные с диабетом	Skin changes associated with insulin resistance / Изменения кожи, связанные с резистентностью к инсулину	Complications of insulin therapy/ Осложнения инсулинотерапии
• Xerosis / Ксероз • Follicular hyperkeratosis / Фолликулярный гиперкератоз • Fungal and bacterial infections / Инфекции грибковые и бактериальные • Microangiopathies and neuropathies / Микроангиопатии и нейропатии	• Granuloma annulare / Кольцевидная гранулема • Necrobiosis lipoidica / Липоидный некробиоз • Diabetic dermopathy / Диабетическая стопа • Onychodystrophy / Ониходистрофия • Vitiligo / Витилиго	• Acanthosis nigricans / Черный акантоз • Akrochordone / Акрохордоны • Acne, seborrhea / Угри, себорея	• Lipoatrophy and lipohypertrophy / Липоатрофия и липогипертрофия • Scarring / Рубцы • Blisters / Пузыри

by abnormal collagen glycation during episodes of hyperglycemia or collagen proliferation caused by excess insulin. The limbs appear to be the most vulnerable to benign skin thickening in patients with DM, which is closely related to the subsequent limitation of joint mobility. Even in the absence of visible changes, an increase in skin thickness can be confirmed by ultrasonography [10].

Hyperkeratosis follicularis (keratosis pilaris) is a common (11.7%) condition in patients with T1DM aged >10 years. Clinical manifestations include coarse follicular papules and erythema, located predominantly on the extensor surfaces of the arms and legs, sometimes on the face, buttocks, and trunk. Keratosis pilaris tends to be aggravated in winter and less severe in the summer months.

The so-called *face redness in patients with DM* (Rubeosis faciei diabeticorum) is a characteristic rash on the face noted in some patients, which is caused by dilatation of small vessels on the cheeks, probably as a result of diabetic microangiopathy [41]. The prevalence of this condition increases with the disease duration and is more common in patients with T2DM (51%) than in pediatric patients with T1DM (7%) [44].

Limited joint mobility, also called diabetic arthropathy, is the most clinically evident long-term complication of childhood T1DM [30]. It is characterized by asymptomatic bilateral contracture of the finger joints (chaeropathy) associated with waxy thickening of the skin. In more severe cases, the process involves the cervical spine, large joints of the limbs, and feet. This appears to be the result of non-enzymatic glycation of collagen, which leads to the formation of insoluble cross-linked collagen causing rigidity in the dermis and joints. The incidence rate of this complication (2.3%–30%) [10, 44] increases with the T1DM duration (>5 years), age (usually develops in prepubertal and pubertal age), and decreases due to improved glycemic control [5, 6]. Following the first manifestations, the disease progresses over several months or years, after which the pathological process is stabilized [41].

Patients with limited joint mobility are at increased risk of other microvascular complications of DM, especially retinopathy and neuropathy.

Infections. Patients with DM are prone to severe, recurrent, and atypical infections. DM causes changes in the immune system such as a decrease in the chemotaxis of leukocytes and phagocytosis, a significant deficit of the immune response due to impairment of the vascular reaction which contributes to the occurrence of infections and a delay in their resolution [36]. In children with DM, candidiasis is most common, and dermatophytosis is less often reported. Moreover, no association with viral skin diseases was noted. Candidal infection in the form of vulvovaginitis, balanitis, and angular cheilitis is reported more often in patients with DM than in the general population [6, 44]. Candidal vulvovaginitis accounts for up to 56% of infection cases of the external genital organs in girls with DM aged 2–15 years [10]. Among bacterial infections, staphyloderma and streptoderma infections are predominant, whereas staphylococcal infections occur more often in patients with T1DM than in those with T2DM [37, 38]. Folliculitis and impetigo are the most common infections in carriers of *Staphylococcus aureus*.

Microangiopathy and neuropathy. DM gradually affects the vascular and nervous system because it is associated with structural changes in tissues due to chronic hyperglycemia as well as ischemia. Microangiopathies are found more often in the second decade of life and associated with reduced elasticity and impaired endothelial function of peripheral arteries [6]. Lesions of the lower extremities include hypothermia, nail dystrophy, patchy skin color, and hair loss on the legs. Other manifestations are anhidrosis, which is a result of severe vascular or autonomic dysfunction, and poor wound healing due to vascular insufficiency and neuropathy. The most severe lesion of the lower extremities in DM, the so-called diabetic foot, is usually registered in older patients; however, in adolescents and young people, there can be changes that predispose to the development of a diabetic foot, namely helomas, ingrown nails, blisters, dryness, hypothermia, and skin dystrophy. These predisposing factors must be necessarily identified and preventive measures must be taken [30].

Skin diseases that are more common in patients with DM. There is a group of disorders of unknown etiology that are associated with DM or are more common in patients with DM. These are necrobiosis lipoidica, granuloma annulare, and diabetic dermopathy.

Necrobiosis lipoidica is a rare disease even among patients with DM, which is more common in women than in men and adults than in children (0.3% and 0.06%, respectively) [10].

Meanwhile, in 2007, M.D. Pavlović reported that necrobiosis lipoidica occurs in 2.3% of patients with T1DM and did not confirm a significant relationship among skin lesions, age, disease duration, and metabolic control [44]. Clinically, necrobiosis lipoidica manifests itself as bilateral,

asymptomatic, and yellow-orange or red-brown plaques located symmetrically on the lower extremities (often on the front of the lower leg) or in some cases on the upper extremities. Typical histological signs include neutrophilic necrotizing vasculitis in the early stages, amorphous degeneration, and hyalinization of cutaneous collagen (necrobiosis) in later stages. Treatment includes good blood glucose control.

Granuloma annulare is a benign inflammatory disease characterized by the degeneration of connective tissue and predominantly histiocytic inflammatory infiltration. Although the origin of this condition remains poorly understood, in adults, this condition is associated with several systemic diseases, especially rheumatic diseases and DM. In children, such associations were not noted, but the literature presents data on individual cases of granuloma annulare in children with DM [36]. Granuloma annulare can occur at any age, but it is generally more common in children and adolescents. In children, the most common clinical variants are localized and subcutaneous forms. Localized granuloma annulare appears as dense and smooth pale pink papules. Papules coalesce into one or more annular plaques around a slightly depressed pallid center [10, 36].

In some patients, granuloma annulare may coexist with necrobiosis lipoidica. Their histological similarity makes some researchers believe that granuloma annulare is an early phase of necrobiosis lipoidica. Treatment is often not required, as most rashes resolve spontaneously within 2 years.

Diabetic dermopathy is the most common cutaneous manifestation of DM in adults (9%–55%) and is relatively rare in children. It presents as clearly defined, slightly indented, light-brown atrophic spots, usually <1 cm in diameter. Lesions are usually localized on the anterior surface of the lower legs and lateral sides of the ankles and are less often on the thighs and arms. These lesions are usually bilateral or asymmetric. Although the etiology and pathogenesis of this condition are poorly understood, clinical manifestations are caused by hemosiderin and melanin deposits in the dermis. The histological pattern in the epidermis includes atrophy, moderate hyperkeratosis, and varying degrees of basal pigmentation. In the papillary dermis, telangiectasis, fibroblast proliferation, edema, hyaline microangiopathy, extravasated erythrocytes, hemosiderin deposits, and moderate perivascular infiltrate consisting of lymphocytes, histiocytes, and plasma cells are detected [10, 36].

Such dermopathy requires ruling out DM because it is closely related to DM and specific to it. The presence of dermopathy in patients with DM is an indicator that the disease is poorly controlled [37].

Vitiligo. According to the literature, vitiligo is registered in 1%–7% of patients with DM (and only in 0.2%–1% of the general population), and DM is diagnosed in 0.6% of patients with vitiligo [30, 35]. Vitiligo associated with DM often occurs in a generalized form that is resistant to treatment [30].

Cutaneous manifestations of insulin resistance syndrome. In recent years, the growing prevalence of insulin resistance syndrome and the worldwide increase in the incidence of T2DM are concerning. Insulin resistance is a condition when a certain amount of insulin does not elicit the expected biological response, followed by compensatory hyperinsulinemia to maintain normal glucose levels and lipid homeostasis [45]. Insulin resistance is a risk factor for DM and heart and central nervous system diseases. The most common cutaneous manifestations of insulin resistance are acrochordons and acanthosis nigricans. These disorders are reported in one-third of patients.

Acanthosis nigricans is the most common early sign of obesity and/or insulin resistance syndrome in children [10, 51, 53]. The etiology and pathogenesis of acanthosis nigricans have not been completely elucidated; however, data indicate the involvement of insulin in this process. Increased proliferation of epidermal cells in acanthosis nigricans is clearly associated with hyperinsulinemia and insulin resistance; an increased plasma insulin level was recorded in 74% of patients with obesity and acanthosis nigricans [25]. Acanthosis nigricans can develop under the influence of insulin-like growth factor-1 (IGF-1), which is overproduced by the liver due to hyperinsulinemia. IGF-1 receptors are expressed on basal keratinocytes and fibroblasts and are stimulated in similar proliferative conditions [36]. In the beginning, hyperpigmentation usually appears, later accompanied by hypertrophy of the skin, with a further intensification of its color, and papillomatosis. Most often, the process is localized in the armpits, on the rear and lateral surfaces of the neck, in the area of the external genital organs, and the inner surface of the thighs (Fig. 1).

Acrochordons (soft fibroma and fibroepithelial polyp) manifest as benign proliferative formations on the skin. They are represented by soft papules on pedicles of brownish or skin color, most often located in the armpits, groin areas, and neck. Me-

chanical friction, endocrine disorders, and human papillomavirus (HPV) are considered contributing factors. HPV infection begins with the inoculation of the virus into the viable epidermis at the sites of its damage, and infection further spreads because of autoinoculation [53].

Other skin manifestations include keratosis pilaris, hirsutism, and signs of hyperandrogenism such as acne and seborrhea, which are aggravated by obesity.

Skin disorders associated with insulin therapy. Information on the prevalence of skin complications caused by insulin injection varies; in one study, lipohypertrophy was detected in 1.8% of cases, but two other studies reported lipoatrophy and lipohypertrophy in 29% and 48% of the patients, respectively [10, 30]. Refusal to rotate injection sites is considered an independent risk factor for the development of lipohypertrophy [6].

Other post-injection skin changes can be redness, vesicular rashes, and local infection. In the literature, the most common complications of constant subcutaneous insulin infusion (insulin pump therapy) in children are scars (<3 mm), erythema, subcutaneous nodules, and lipohypertrophy.

Obesity

Obesity is a heterogeneous group of hereditary and acquired diseases associated with excessive accumulation of adipose tissues in the body. A study reported that the number of patients with obesity has increased in recent years [47]. Obesity is associated not only with an increased risk of such diseases serious as DM, atherosclerosis, and hypertension but also participates in the development of various dermatological diseases, in both adults and children [1, 2, 47, 49, 53]. Since the amount of adipose tissue is difficult to calculate, to diagnose obesity, body mass index (BMI) is used, which is the ratio of body weight in kilograms to the square of height in meters. BMI correlates with the amount of adipose tissue in the body in both adults and children (assessment in children should consider gender and age). A patient with BMI over the 95th percentile, or 2 standard deviation score (SDS), is diagnosed with obesity, and overweight is established with BMI corresponding to the 85–95th percentile, or 1–2 SDS [6]. Although the exact prevalence of cutaneous manifestations of obesity is unknown, they are directly related to the severity and duration of metabolic disorders. In addition, the combination of obesity with DM and/or insulin resistance syndrome increases the probability of dermatological diseases [10, 53].

Obesity affects the physiological processes in the skin, including the effect on its barrier function, functioning of the sebaceous and sweat glands, lymphatic and collagen structure of the skin, wound healing, microcirculation, and subcutaneous fat [33, 42].

Yosipovitch et al. [53] classified the skin changes in obesity (adapted for children).

Diseases associated with insulin resistance are as follows:

- Insulin resistance syndrome.
- Acanthosis nigricans.
- Acrochordons.
- Keratosis pilaris.
- Acne.
- Hirsutism.

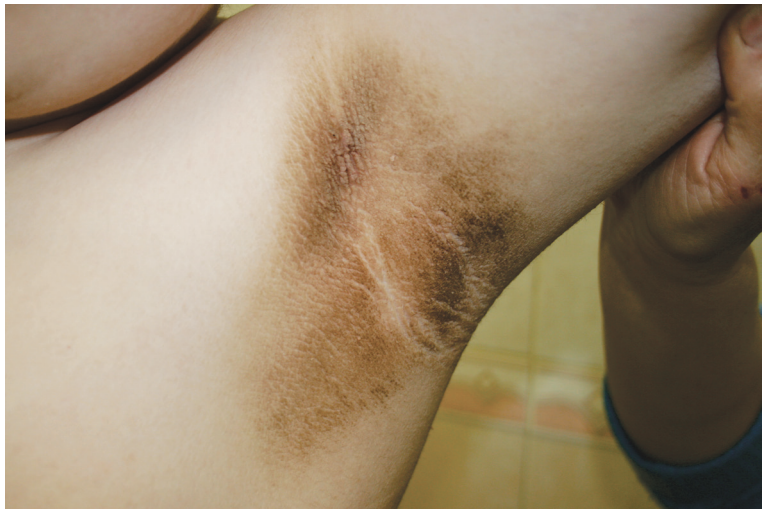

Fig. 1. Acanthosis nigricans in an obese patient

Рис. 1. Acanthosis nigricans (черный акантоз) у пациента с ожирением

Diseases associated with mechanical action on the skin:
- Plantar hyperkeratosis.
- Striae.

Infectious diseases
- Intertrigo.
- Candidiasis.
- Dermatophytosis.
- Folliculitis.

Inflammatory diseases:
- Psoriasis.
- Hydradenitis.

In recent studies, the majority of patients with obesity have plantar hyperkeratosis (47%), striae (68%), acrochordons (48%), intertrigo (44%), and less often acanthosis nigricans [12, 18]. Psoriasis in patients with obesity is detected five times more often than that in the control group [12, 21].

A recent study involved 40 patients with overweight and 25 with obesity aged 7–15 years; the control group consisted of 30 children with normal body weight. Acrochordons were detected in 40% of patients with obesity and in 2.5% patients with overweight, striae were registered in 32% and 22.5% patients, respectively, while plantar hyperkeratosis was noted only in patients with obesity (20%).

Horseshoe-shaped plantar hyperkeratosis, located on the posterior part of the sole, was the most frequent cutaneous manifestation in patients whose weight was excessive by more than 176%, and it can be considered a physiological response to mechanical trauma [11, 18].

Striae (stretch marks) are a particular form of skin atrophy, mainly in the places of its greatest stretching. Usually, striae are located symmetrically on the thighs (73%), shoulders (42%), and abdomen (30%) and less often on the chest and buttocks [24]. They have a length of 1–1.5 to 8–10 cm and a width of 1–2 to 5–6 mm, located flush with the skin, or have a retracted relief (Fig. 2).

The color of striae gradually, over several months, changes from bright pink, sometimes even purple, to whitish, with a pearlescent tint. Striae occur not only in obesity but also in conditions such as pregnancy and Cushing syndrome, and during treatment with topical corticosteroids. In the literature, striae in obese individuals are not as wide and atrophic as in patients with Cushing syndrome [8]. The exact pathogenesis of striae has not been elucidated; however, mechanical, hormonal, and genetic factors may play a role in their development [18].

Keratosis pilaris (hyperkeratosis follicularis) presents as small follicular papules (pinhead-sized, with vellus hair on the surface), usually localized on the extensor surfaces of the shoulders and hips. There may be a hyperemic corolla around the papules. When stroking the keratosis area, there is a symptom of "grater" or "sandpaper" [52]. In addition to obesity, follicular hyperkeratosis is noted in Cushing syndrome, DM, and hypothyroidism. Insulin resistance may play a role in the development of keratosis pilaris [53].

Additionally, hyperinsulinemia (as a consequence of insulin resistance) increases the production of androgens and decreases the production of sex hormone-binding globulin by the liver, which, in turn, may contribute to the development of acne, hirsutism, and androgenic alopecia [17, 47].

Obesity increases the incidence of skin infections such as candidiasis, dermatophytosis, and bacterial infections. Although infectious dermatoses are not specific to obesity, the incidence of skin infections

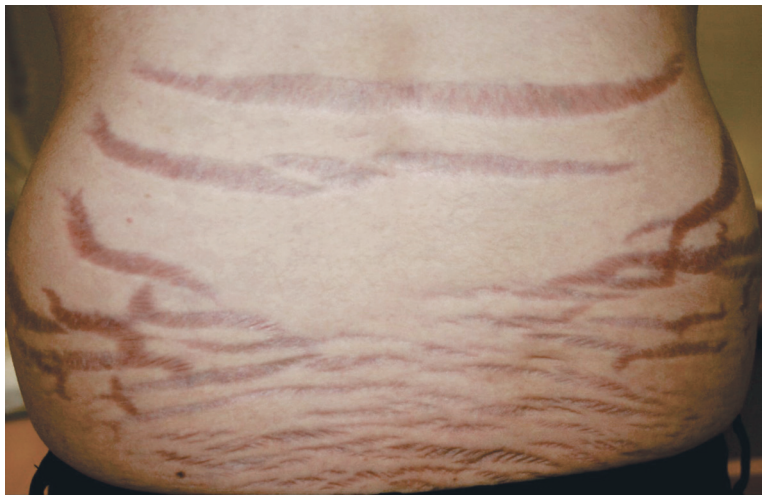

Fig. 2. Striae in a 14-year-old obese girl
Рис. 2. Стрии у девочки 14 лет с ожирением

in patients with overweight is higher than in those with normal body weight [18].

Skin folds become a preferable site of infections, where trivial intertrigo first occurs. Features of the skin of patients with obesity such as deep folds, hyperhidrosis, and mechanical friction, create a favorable environment for increasing maceration and subsequent infection [18].

Recent studies have presented a significantly higher prevalence of obesity in patients with psoriasis than in the general population [9, 13, 20, 32]. Moreover, the question of whether psoriasis or obesity is a precursor is still relevant. A study reported follow-up data of 557 patients with psoriasis and showed that the risk of developing psoriasis is not higher in patients with obesity aged <18 years than in patients without obesity, but obesity later appears in patients with psoriasis (Fig. 3) [22].

Studies have shown that the BMI value is directly related to the duration of psoriasis [46]. The lack of physical activity in patients with psoriasis, associated with a cosmetic defect or arthropathy, probably predisposes them to obesity. Studies have indicated that obesity, hyperlipidemia, hypertension, DM, metabolic syndrome, and polycystic ovary syndrome were more common in the families of patients with psoriasis than in the control group [34, 35, 50, 52]. A study showed that patients with psoriasis were more likely to be overweight than children in the control group (37.9 and 20.5%, respectively) [43]. Moreover, the onset of childhood obesity especially predisposes the patients to the development of psoriasis and psoriatic arthropathy, which probably reflects the influence of genetic factors [43]. Among children with obesity, the blood levels of cholesterol, low-density lipoproteins, and triglycerides were significantly higher in patients with psoriasis than in those without it [29]. Clinical cases confirm the presence of common signs in the pathogenesis of obesity and psoriasis. Macrophages in adipose tissue produce tumor necrosis factor (TNF)-α, as well as other cytokines (interleukin [IL]-1, IL-6, IL-17, and interferon-γ) involved in the development of psoriasis [3, 13, 19]. Adipocytes produce adipokines (adipocytokines), namely leptin, resistin, and adiponectin [4]. Cytokines and leptin accumulate in case of obesity and can have autocrine and paracrine effects on nearby skin. Leptin affects T-cell regulation and stimulates the release of pro-inflammatory cytokines [3]. The blood concentration of leptin correlates with the severity of psoriasis [14, 19]. The hormone resistin leads to insulin resistance and promotes the activation of inflammatory processes in the skin. The level of

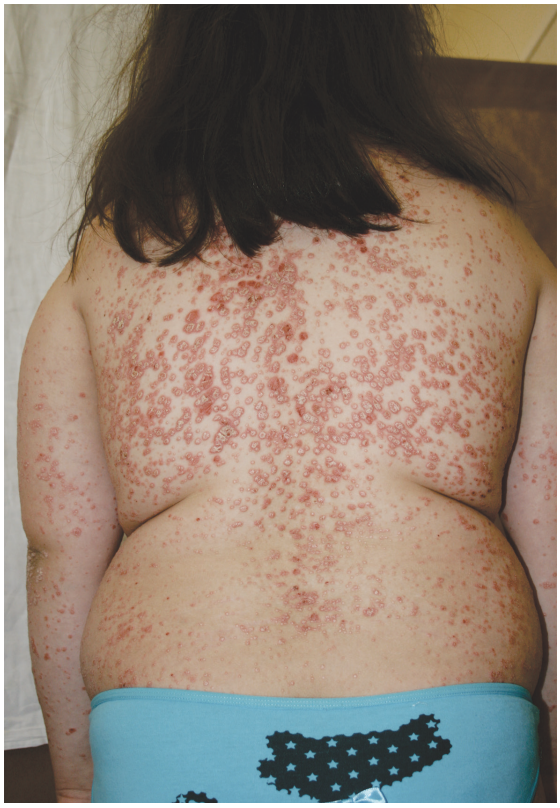

Fig. 3. Psoriasis in a 14-year-old obese girl
Рис. 3. Псориаз у девочки 14 лет с ожирением

resistin is increased in patients with psoriasis (directly dependent on the disease severity) and correlates with the BMI [24]. The level of the anti-inflammatory mediator adiponectin in patients with psoriasis and obesity is lower than that in patients with psoriasis and normal body weight [16]. Thus, immunological and metabolic disorders associated with obesity may be associated with the pathogenesis of psoriasis [14, 16, 19, 27]. The so-called inverse psoriasis (psoriasis in the folds) was recorded more often in the obese group than in the control group (11% and 5%, respectively) [22].

Studies have presented numerous data on the relationship between obesity and atopic dermatitis (AD) [15, 48, 52], and researchers revealed that the incidence of AD is significantly higher in patients with obesity, especially with manifestation at the age of up to 2 years, than in the control group. The duration of obesity (more than 2.5 years) also increased the probability of AD [39]. The association of AD with obesity is possibly due to various immune disorders detected in obesity, especially with the production of TNF-α and IL-6 by adipocytes. Leptin, which is produced by adipocytes, has a pro-inflammatory effect on the immune system, causing the proliferation and activation of monocytes

and CD4 and CD8 lymphocytes, and polarizing the T-cell response toward TH1 [17, 40].

Cushing syndrome

Cushing syndrome represents a combination of clinical symptoms caused by a chronic increase in the levels of cortisol or related corticosteroids in the blood. Although Cushing syndrome is predominant in female adolescents and adults, in the prepubertal period, boys are affected by it more often than girls. Most of the children with Cushing syndrome are obese in the trunk and have growth retardation [6]. Excessive glucocorticoid levels are believed to decrease the proliferation of keratinocytes and dermal fibroblasts, which in turn leads to decrease in the formation of collagen and other components of the extracellular matrix and ultimately contributes to skin atrophy and fragility. The catabolic effect of glucocorticoids extends to subcutaneous connective tissues. Cutaneous manifestations of Cushing syndrome are as follows [31]:

- Moonlike face.
- Striae.
- Cigarette paper atrophy of the skin on the elbows and dorsum of the hands.
- Slow wound healing.
- Steroid acne.
- Hyperpigmentation.
- Acanthosis nigricans.

Fatty tissue is often deposited on the face in the cheeks (moonlike face), on the posterior surface of the neck with the transition to the back (dorsocervical fat), above the collarbones (thick, short neck), and behind the orbit (exophthalmos). Cigarette paper skin on the elbows and the dorsal side of the hands is a result of epidermal and cutaneous atrophy. As body weight is redistributed and increased, the fragile skin stretches and subcutaneous blood vessels become more visible, looking like purple striae. In Cushing syndrome, the flaccid and wide (>1 cm in diameter) striae can be distinguished from the pinkish-silver thin striae seen in growth spurt, obesity, and pregnancy. Additional changes in the skin may appear in the form of acanthosis nigricans. An excess in the levels of endogenous or exogenous glucocorticoids can lead to steroid acne localized on the upper back, proximal upper limbs, neck, and face. Excess glucocorticoids can also lead to superficial dermatophytosis and malassezia infection.

Polycystic ovary syndrome

Polycystic ovary syndrome is characterized by the excessive production of androgens, which can manifest in adolescent girls as menstrual irregularities, android type obesity, and skin changes, such as acne and/or hirsutism [28, 31]. Initial screening for suspected androgen-associated disease is usually serum dehydroepiandrosterone sulfate, testosterone, and prolactin tests [31]. Cutaneous manifestations in hyperandrogenemia are as follows [28, 31]:

- Acne.
- Hirsutism.
- Androgenic alopecia.
- • Acanthosis nigricans.

Hirsutism is defined as excessive growth of terminal hairs in androgen-dependent areas, primarily the face, neck, back, chest, and lower abdomen [6, 28]. Hyperandrogenism promotes an increase in hair thickness and prolongs the phase of hair growth in the beard, armpits, and pubis. Acne vulgaris is an additional manifestation of polycystic ovary syndrome. The possibility of excess in androgen levels in patients with moderate to severe acne should be considered, especially acne that is resistant to traditional treatments or recurrence after the use of isotretinoin. Signs of severe hyperandrogenism are coarsening of the voice, muscle hypertrophy, breast size reduction, and androgenic alopecia. Patients with androgenic alopecia often notice a gradual thinning of the hair in the parietal region, while maintaining the front hair growth line [23, 27].

Hypothyroidism

Hypothyroidism can be congenital or acquired. Congenital hypothyroidism occurs in 1 per 2000–4000 newborns and is most often associated with thyroid dysgenesis. In the general population, autoimmune thyroiditis (AIT) is the most well-known cause of hypothyroidism worldwide. The incidence of AIT among schoolchildren reaches 1%–2%, and it affects girls 4–7 times more often than boys [6]. The clinical symptoms of hypothyroidism are of low specificity. Meanwhile, changes in the skin and its appendages as well as in the subcutaneous tissue require the exclusion of hypothyroidism, for which, in most cases, it is sufficient to determine the serum level of thyroid-stimulating hormone. Changes in the skin, subcutaneous tissue, and dermal appendages characteristic of hypothyroidism [6, 31] are as follows:

- Pale and subicteric skin.
- Dry, flaky, rough, and cold skin.
- Edematous face and tongue and edema in the area of the supraclavicular fossa and dorsum of the hands and feet.
- Loss of the lateral surfaces of the eyebrows.
- Dry and brittle hair or alopecia.

Hyperthyroidism

Hyperthyroidism is an integral sign of diffuse toxic goiter (DTG), or Graves' disease. In the pediatric population, the peak incidence is recorded at age 10–15 years, and similar to adults, DTG prevails in females. The main cutaneous manifestations of hyperthyroidism are as follows [31]:

- Warm moist thin skin.
- Erythema of the palms.
- Hyperhidrosis.
- Thin hair on the head.
- Onycholysis.
- Pretibial myxedema.
- General pruritus.
- Chronic urticaria.

The most common cutaneous manifestations of hyperthyroidism include facial flushing, palmar erythema, and hyperhidrosis of the palms and plantae. The hair on the head is thin and may fall out. Nails are thin; in rare cases (atypical for children), onycholysis (detachment of the nail plate from soft tissues) can be noted, when the proximal part of the plate remains pink, and the distal part becomes white or opaque (Plummer's nail). Pretibial myxedema is recorded in 4% of patients with Graves' disease (extremely rare in children). Indurations, deepened nodules, and plaques appear on the skin in the tibial area, with hyperpigmentation and desquamation.

Skin changes such as generalized pruritus and eczematous dermatitis are less common in hyperthyroidism. Chronic urticaria (as well as pretibial myxedema) should be considered a possible manifestation of autoimmune disease in DTG, not a consequence of hyperthyroidism.

Acromegaly

Excess growth hormone generates a cascade of clinical manifestations involving soft tissues and bones. Depending on whether hypersomatopinemia is registered before or after the fusion of the epiphyseal growth zones, the disease is defined as gigantism or acromegaly. Pituitary gigantism can be manifest by accelerated growth and tall stature at any age, and cases have been described from month 2 of life. Meanwhile, the incidence of gigantism is extremely low; one major study showed that hypersomatopinemia is found in 0.6% of pituitary adenomas in children and may be a consequence of neurofibromas of the central nervous system. Changes in the skin, as well as soft tissues and dermal appendages, typical for patients with closed growth zones, can also be seen in older adolescents with nearly complete growth and/or in controls in whom the growth hormone is no longer of the same significance [26, 31]:

- Macrocheilia.
- Macroglossia.
- Gingival hyperplasia.
- Coarse facial features.
- Hyperpigmentation.
- Acanthosis nigricans.
- Hyperhidrosis.
- Hypertrichosis.
- Nail changes.

CONCLUSIONS

Skin lesions are quite common in endocrine diseases. This fact must be kept in mind by pediatricians, dermatologists, and endocrinologists.

REFERENCES

1. Абдулхабирова Ф.М., Абросимов А.Ю., Александрова Г.Ф., и др. Эндокринология: Российские клинические рекомендации. – М.: ГЭОТАР-Медиа, 2016. – 592 с. [Abdulhabirova FM, Abrosimov AJu, Aleksandrova GF, et al. *Jendokrinologija: Rossijskie klinicheskie rekomendacii*. Moscow: GJeOTAR-Media, 2016. 592 p. (In Russ.)]
2. Горланов И.А., Леина Л.М., Милявская И.Р., Заславский Д.В. Болезни кожи, ассоциированные с ожирением // Вестник дерматологии и венерологии. – 2016. – Т. 92. – № 6. – С. 20–26. [Gorlanov IA, Zaslavskiy DV, Leina LM, Milyavskaya IR. Obesity related skin disorders. *Vestnik Dermatologii i Venerologii*. 2016;92(6):20-26. (In Russ.)]
3. Ковалева О.А., Амбросова Т.Н., Ащеулова Т.В. Адипокины: биологические, патофизиологические и метаболические эффекты // Внутренняя медицина. – 2009. – № 3. – С. 15–23. [Kovaleva OA, Ambrosova TN, Ashheulova TV. Adipokiny: biologicheskie, patofiziologicheskie i metabolicheskie jeffekty. *The Russian Archives of Internal Medicine*. 2009;(3):15-23. (In Russ.)]
4. Петренко Ю.В., Герасимова К.С., Новикова В.П. Биологическая и патофизиологическая значимость адипонектина // Педиатр. – 2019. – Т. 10. – № 2. С. – 83–87. [Petrenko YV, Gerasimova KS, Novikova VP. Biological and pathophysiological role of adiponectin. *Pediatrician (St. Petersburg)*. 2019;10(2):83-87. (In Russ.)] https://doi.org/10.17816/PED10283-87
5. Строев Ю.И., Чурилов Л.П. Эндокринология подростков. – СПб.: Медкнига «ЭЛБИ», 2004. – 384 с. [Stroev JuI, Churilov LP. Jendokrinologija podrostkov. Saint Petersburg: Medkniga "JeLBI", 2004. 384 p. (In Russ.)]
6. Шабалов Н.П., ред. Диагностика и лечение эндокринных заболеваний у детей и подростков: учебное пособие, 4-е изд. – М.: МЕДпресс-информ, 2018. [Shabalov NP, editor. Diagnostika i lechenie

jendokrinnyh zabolevanij u detej i podrostkov: uchebnoe posobie, 4-e izd. M.: MEDpress-inform Publ., 2018. (In Russ.)]
7. Шаповалова А.Б., Шершнёв А.А. Неаутоиммунные формы диабета у детей и подростков: новые ответы в вопросах факторов риска и диагностики // Медицина: теория и практика. – 2021. – Т. 6. – № 1. – С. 3–14. [Shapovalova AB, Shershnev AA. Non-autoimmune forms of diabetes in children and teens: new answers in questions of risk factors and diagnostics. *Medicine: theory and practice*. 2021;6(1):3-14. (In Russ.)]
8. Angeli A, Boccuzzi G, Frajria R, Bisbocci D. Adrenal gland function test in the differential diagnosis of sthenic obesity with pink striae. *Folia Endocrinol*. 1970;23:566-578.
9. Augustin M, Radtke MA, Glaeske G, et al. Epidemiology and Comorbidity in Children with Psoriasis and Atopic Eczema. *Dermatology*. 2015;231(1):35-40. https://doi.org/10.1159/000381913
10. Baselga-Torres E, Torres-Pradilla M. Cutaneous manifestations in children with diabetes mellitus and obesity. *Actas Dermosifiliogr*. 2014;105(6):546-557. https://doi.org/10.1016/j.adengl.2014.05.016
11. Birtane M, Tuna H. The evaluation of plantar pressure distribution in obese and non-obese adults. *Clin Biomech*. 2004;19(10):1055-1059. https://doi.org/10.1016/j.clinbiomech.2004.07.008
12. Boza JC, Trindade EN, Peruzzo J, et al. Skin manifectations of obesity: a comparative study. *J Eur Acad Dermatol Venereol*. 2012;26(10):1220-1223. https://doi.org/10.1111/j.1468-3083.2011.04265.x
13. Bremer S, Van Voorhess AS, Hsu S, et al. Obesity and psoriasis: from the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol*. 2010;63(6):1058-1069. https://doi.org/10.1016/j.jaad.2009.09.053
14. Ceman AA, Bozkurt S, Sav A, et al. Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. *Br J Dermatol*. 2008;159(4):820-826. https://doi.org/10.1111/j.1365-2133.2008.08742.x
15. Chen Y, Rennie D, Cormier Y, Dosman J. Association between obesity and atopy in adults. *Int Arch Allergy Immunol*. 2010;153(4):372-377. https://doi.org/10.1159/000316348
16. Coimbra S, Oliveira H, Reis F, et al. Circulating adipokine levels in Portugese patients with psoriasis vulgaris according to body mass index, severity and therapy. *J Eur Acad Dermatol Venereol*. 2010;24(12):1386-1394. https://doi.org/10.1111/j.1468-3083.2010.03647.x
17. Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol*. 2005;115(5):911-920. https://doi.org/10.1016/j.jaci.2005.02.023
18. Garcia-Hidalgo L, Orozco-Torete R, Gonzalez-Barranco J, et al. Dermatoses in 156 obese adults. *Obes Res*. 1999;7(3):299-302. https://doi.org/10.1002/j.1550-8528.1999.tb00410.x
19. Gerdes S, Rostami-Yazdi M, Mrowietz U. Adipokines and psoriasis. *Exp Dermatol*. 2011;20(2):81-87. https://doi.org/10.1111/j.1600-0625.2010.01210.x
20. Guidolin L, Borin M, Fontana E, et al. Central Obesity in Children with Psoriasis. *Acta Derm Venereol*. 2018;98(2):282-283. https://doi.org/10.2340/00015555-2816
21. Hercogova J, Ricceri F, Tripo L, et al. Psoriasis and body mass index. *Dermatol Ther*. 2010;23(2):152-154. https://doi.org/10.1111/j.1529-8019.2010.01309.x
22. Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. *Arch Dermatol*. 2005;141(12):1527-1534. https://doi.org/10.1001/archderm.141.12.1527
23. Housman E, Reynolds RV. Polycystic ovary syndrome: a review for dermatologists: Part I. Diagnosis and manifestations. *J Am Acad Dermatol*. 2014;71(5):847.e-858. https://doi.org/10.1016/j.jaad.2014.05.007
24. Hsu HS, Chen W, Chen SC, Ko FD. Colored striae in obese children and adolescents. *Zhonghua Min Guo. Xiao Er Ke Yi Xue Hui Za Zhi*. 1996;37:349-352.
25. Hud JA Jr, Cohen JB, Wagner JM, Cruz PD Jr. Prevalence and significance of acantosis nigricans in an adult obese population. *Arch Dermatol*. 1992;128:941-944. https://doi.org/10.1001/archderm.128.7.941
26. Jabbour SA. Cutaneous manifestations of endocrine disorders: a guide for dermatologists. *Am J Clin Dermatol*. 2003;4:315-331. https://doi.org/10.2165/00128071-200304050-00003
27. Johnston A, Arnadottir S, Gudjonsson JE, et al. Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. *Br J Dermatol*. 2008;159(2):342-350. https://doi.org/10.1111/j.1365-2133.2008.08655.x
28. Keen MA, Shah IH, Sheikh G. Cutaneous Manifestations of Polycystic Ovary Syndrome: A Cross-Sectional Clinical Study. *Indian Dermatol Online J*. 2017;8(2):104-110. https://doi.org/10.4103/2229-5178.202275
29. Koebnick C, Black MN, Smith N, et al. The association of psoriasis and elevated blood lipids in overweight and obese children. *J Pediatr*. 2011;159(4):577-583. https://doi.org/10.1016/j.jpeds.2011.03.006
30. Kordonouri O, Maguire AM, Knip M, et al. Other complications and associated conditions with diabetes in children and adolescents. *Pediatr Diabetes*. 2009;10(12):204-210. https://doi.org/10.1111/j.1399-5448.2009.00573.x
31. Lause M, Kamboj A, Fernandez Faith E. Dermatologic manifestations of endocrine disorders. *Transl Pediatr*. 2017;6(4):300-312. https://doi.org/10.21037/tp.2017.09.08

32. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. *Dermatologica*. 1986;172(6):298-304. https://doi.org/10.1159/000249365
33. Loffler H, Aramaki JU, Effendy I. The influence of body mass index on skin susceptibility to sodium lauryl sulphate. *Skin Res Technol*. 2002;8(1):19-22. https://doi.org/10.1046/j.0909-752x
34. Mahe E, MacCari F, Beauchet A, et al. Childhood-onset psoriasis: Association with future cardiovascular and metabolic comorbidities. *Br J Dermatol*. 2013;169(4):889-895. https://doi.org/10.1111/bjd.12441
35. Mahé E. Childhood psoriasis. *Eur J Dermatol*. 2016;26(6):537-548. https://doi.org/10.1684/ejd.2016.2932
36. Mendes AL, Miot HA, Haddad V Jr. Diabetes mellitus and the skin. *An Bras Dermatol*. 2017;92(1):8-20. https://doi.org/10.1590/abd1806-4841.20175514
37. Menne EN, Sonabend RY, Mason EO, et al. Staphylococcus aureus infections in pediatric patients with diabetes mellitus. *J Infect*. 2012;65(2):135-141. https://doi.org/10.1016/j.jinf.2012.04.001
38. Morgan AJ, Schwartz RA. Diabetic dermopathy: A subtle sign with grave implications. *J Am Acad Dermatol*. 2008;58(3):447-451. https://doi.org/10.1016/j.jaad.2007.11.013
39. Murray CS, Canoy D, Buchan I, et al. Body mass index in young children and allergic disease: gender differences in a longitudinal study. *Clin Experimental Allergy*. 2010;41(1):78-85. https://doi.org/10.1111/j.1365-2222.2010.03598.x
40. Nagel G, Koenig W, Rapp K, et al. Associations of adipokines with asthma, rhinoconjunctivitis, and eczema in German schoolchildren. *Pediatr Allergy Immunol*. 2009;20(1):81-88. https://doi.org/10.1111/j.1399-3038.2008.00740.x
41. Ngo BT, Hayes KD, DiMiao DJ, et al. Manifestations of Cutaneous Diabetic Microangiopathy. *Am J Clin Dermatol*. 2005;6:225-237. https://doi.org/10.2165/00128071-200506040-00003
42. Nino M, Franzese A, Ruggiero-Perrino N, Balato N. The effect of obesity on skin disease and epidermal permeability barrier status in children. *Pediatr Dermatol*. 2012;29(5):567-570. https://doi.org/10.1111/j.1525-1470.2012.01738.x
43. Paller AS, Mercy K, Kwasny MJ, et al. Association of pediatric psoriasis severity with excess and central adiposity: an international cross-sectional study. *JAMA Dermatol*. 2013;149(2):166-176. https://doi.org/10.1001/jamadermatol.2013.1078
44. Pavlović MD, Milenković T, Dinić M, et al. The prevalence of cutaneous manifestations in young patients with type 1 diabetes. *Diabetes Care*. 2007;30(8):1964-1967. https://doi.org/10.2337/dc07-0267
45. Poeggeler B, Schulz C, Pappolla MA, et al. Leptin and the skin: a new frontier. *Exp Dermatol*. 2010;19(1):12-18. https://doi.org/10.1111/j.1600-0625.2009.00930.x
46. Sakai R, Matsui S, Fukushima M, et al. Prognostic factor analysis for plaque psoriasis. *Dermatology*. 2005;211(2):103-106. DOI: 10.1159/000086437
47. Shipman AR, Millington GWM. Obesity and the skin. *Br Dermatol*. 2011:165(4):743-750. https://doi.org/10.1111/j.1365-2133.2011.10393.x
48. Silverberg JI, Kleiman E, Lev-Tov H, et al. Association between obesity and atopic dermatitis in childhood: A case-control study. *J Allergy Clin Immunol*. 2011;127(5):1180-1186. https://doi.org/10.1016/j.jaci.2011.01.063
49. Tobin A, Ahern T, Rogers S, et al. The dermatological consequences of obesity. *Int J Dermatol*. 2013;52(8):927-932. https://doi.org/10.1111/j.1365-4632.2012.05624.x
50. Tollefson MM, Van Houten HK, Asante D, et al. Association of Psoriasis With Comorbidity Development in Children With Psoriasis. *JAMA Dermatol*. 2018;154(3):286-292. DOI: 10.1001/jamadermatol.2017.5417
51. Torley D, Bellus GA, Munro CS. Genes growth factors and acantosis nigricans. *Br J Dermatol*. 2002;147(6):1096. DOI: 10.1046/j.1365-2133.2002.05150.x
52. Yosipovitch G, Mevorah B, Mashiach J, et al. High body mass index, dry scaly leg skin and atopic conditions are highly associated with keratosis pilaris. *Dermatology*. 2000;201(1):34-36. DOI: 10.1159/000018425
53. Yosipovitch G, DeVore A, Dawn A. Obesity and skin: skin physiology and skin manifestations of obesity. *J Am Acad Dermatol*. 2007;56(6):901-916. DOI: 10.1016/j.jaad.2006.12.004

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