Vitiligo and other hypopigmentation disorders in children and adolescents

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The loss of pigment, either partial (hypopigmentation) or complete (depigmentation), can have a major psychological impact on patients. Hypopigmentation disorders, congenital and acquired, are very numerous, and many of them are rarely seen. This paper provides an overview of the most common hypopigmentation disorders in children and adolescents, stressing the importance of vitiligo and autoimmune disorders in patients. Vitiligo is an acquired disease, possibly of autoimmune nature, sometimes with a clear hereditary component, which is characterized by progressive, clearly defined, milky white spots on the skin and/or mucous membranes. In about 50% of patients vitiligo occurs before 20 years of age. The clinical picture of vitiligo in children and adolescents is similar to adults, but there are some differences in the epidemiology, their associations with other endocrine and/or autoimmune diseases and treatment of vitiligo in children compared to adult patients.

Key words: Hypopigmentation, Vitiligo, Child, Adolescent, Diagnosis.

Introduction

Pigmentation disorders can be congenital or acquired. Congenital disorders of pigmentation, often result from mutations of many genes that govern the processes of development of melanoblasts, their migratory movements towards the periphery, and their differentiation into mature melanocytes that produce pigment. The acquired pigmentation disorders are mainly due to qualitative or quantitative defects of melanocytes (e.g. vitiligo) in the skin and mucous membrane (1, 2).

The loss of pigment, either partial (hypopigmentation) or complete (depigmentation), can have a major psychological impact on patients. In many religious writings, depigmentation is described as a sign of dangerous, communicable diseases (3). In ancient times, vitiligo was equated with leprosy, in which hypopigmentation also occurs, and these patients were varying degrees of social
outcasts (1, 2, 4). Although it is now known that most hypopigmented changes in the skin are not contagious and dangerous, loss of pigment causes psychological problems for a large number of patients (5). Many skin diseases are accompanied by hypopigmentation or depigmentation. Vitiligo, pityriasis alba and pityriasis versicolor and varietas alba are seen in everyday clinical practice, and these diseases will be discussed (6).

Vitiligo

Vitiligo is an acquired disease, possibly autoimmune by nature, sometimes with a clear hereditary component, which is characterized by progressive, clearly circumscribed, milky white spots on the skin and/or mucous membranes. The name vitiligo comes from the Latin *vitium* (anomaly) or *vitelius* (white patches on calf’s fur) (1, 2, 3).

The etiology and pathogenesis of vitiligo

The etiology and pathogenesis of vitiligo is not fully explained. It is known that genetic factors play a role in the development of vitiligo: a positive family history in up to 30% of patients, described cases of vitiligo in twins, and the fact that vitiligo occurs with diseases that have a clear genetic basis, such as diabetes mellitus, suggests that role (3, 4, 13). Recent research suggests two possible modes of inheritance of vitiligo, which are associated with the age at which vitiligo appeared (14). In patients with early onset of vitiligo (before age 30), vitiligo is caused by the dominant mode of inheritance with incomplete penetration. However, in patients with late onset (after age 30), predisposition to vitiligo is the result of a recessive genotype and the influence of the external environment (15, 16). An earlier start of vitiligo (up to 7 years) was found in children with vitiligo and a positive family history of vitiligo (17). There is clear evidence of the association of certain MHC haplotypes with a positive family history of vitiligo, onset timing, severity of disease and ethnic origin (15, 16). As a possible theory for the etiology of vitiligo the following are cited: the autoimmune, oxidative stress theory (theory of self-destruction of melanocytes) and the neurogenic theory (1, 2, 3, 4).

The autoimmune theory is supported by experimental evidence and clinical association with other autoimmune diseases: pernicious anemia, Addison’s disease, type 1 diabetes mellitus (T1DM), juvenile rheumatoid arthritis, alopecia areata and especially Hashimoto’s thyroiditis (1, 3, 18, 19, 20, 21). Vitiligo is relatively common in of autoimmune polyglandular insufficiency syndrome (APS), especially in type I (APS-I), where 25% of patients have vitiligo (22). Patients with vitiligo often have organ-specific serum autoantibodies, especially antithyroid
(antithyroglobulin and antibodies against thyreoperoxidase) and antiparietal auto-
antibodies. Some research suggests that an increased incidence of autoimmune thy-
roiditis in patients with vitiligo is genetically determined. The locus on chromosome 1 -
AIS1 (engl. autoimmunity susceptibility), responsible for the tendency to autoimmune responses, particularly for vitiligo, in the presence of other genes (e.g. the main histo-
compatibility complex localized on the short arm of chromosome 6), combined with ex-
posure to external or internal factors, may mediate in the development of Hashimoto’s thyroditis in patients whose AIS1 is sus-
ceptible (23, 24). It is known that genes on chromosome 17p13 contribute to the de-
velopment of certain autoimmune diseases, which include generalized vitiligo, autoim-
mune thyroiditis, T1DM, rheumatoid arthritis, psoriasis, pernicious anemia, sys-
temic lupus erythematosus, and Addison’s disease. Recent studies describe the NALP1 protein as a gene that regulates the intact-
ess of the immune system. Changes in the DNA sequence in the NALP1 domain, are
associated with an increased risk of general-
ized vitiligo and/or other joint autoimmune diseases, such as autoimmune thyroiditis (25). It is believed that autoimmune mecha-
nisms play a key role in the pathogenesis of non- segmental vitiligo (4).

The melanocytes of active vitiligo reveal an increase in oxidants and antioxidant en-
zyme deficit, with resultant oxidative dam-
age to melanocytes (3, 26, 27). The emer-
gence of segmental vitiligo can be best ex-
plained by the neurogenic theory according to which the nerve endings release the neu-
rochemical mediators that inhibit melanogenesis or have toxic effects on melanocytes, destroying them. Microscopic examination and ultrastructural investigations in people with segmental vitiligo showed damage to axons and disrupted neuropeptide balance in vitiligo lesions (27, 28). As possible pro-
voking factors for the occurrence of vitiligo the following are cited: stress, sun burns, recur-
current skin injuries. It is believed that dif-
ferent mechanisms may cause the same phe-
notype: vitiligo is a heterogeneous disease in terms of etiology (2, 4).

Clinical characteristics of vitiligo

The main change in vitiligo is depigmented macula, usually round or oval-shaped, milky
white color, with a diameter of several milli-
meters to several centimeters (1, 2, 3, 4). The
skin surface in vitiligo is smooth. Atypical
maculae (artificial) appear at the site of in-
jury, lacerations, friction and burns and are
the result of Köebner’s phenomenon (1). Vit-

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-segmental vitiligo</th>
<th>Segmental vitiligo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence (%)</td>
<td>72-95</td>
<td>5-8</td>
</tr>
<tr>
<td>Distribution pattern</td>
<td>Symmetrical, not limited to the dermatome</td>
<td>Unilateral, limited to the dermatome</td>
</tr>
<tr>
<td>Onset</td>
<td>Any age</td>
<td>Young age</td>
</tr>
<tr>
<td>Course</td>
<td>Variable, often new lesions occurring during life (progressive course)</td>
<td>Initial rapid progression, then the activity of lesions limited to the period up to 2 years</td>
</tr>
<tr>
<td>Köebner’s phenomenon</td>
<td>Often present</td>
<td>Rarely present</td>
</tr>
<tr>
<td>Association with autoimmune diseases</td>
<td>Frequent</td>
<td>Extremely rare</td>
</tr>
<tr>
<td>Etiology</td>
<td>Probably autoimmune</td>
<td>likely neurochemical</td>
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Vitiligo can occur anywhere on the skin. Pre-dilection sites are around the natural openings - the eyes, mouth, nipples, navel and genitals. In the majority of patients vitiligo lesions first appear on skin exposed to the sun. In vitiligo patients polyosis commonly occurs (“white lock of hair”) and halo nevus (Sutton nevus) (3).

Vitiligo can be divided into the non-segmental and segmental forms of the disease (1, 2, 4, 9). In segmental vitiligo depigmented plaques are limited to a dermatome. The characteristics of these two types of vitiligo are given in Table 1. In clinical practice the generally accepted classification of vitiligo is by Kovacs (3). According to this classification, vitiligo is divided into focal, segmental, generalized, acrofacial and universal types, which differ not only morphologically but also in their natural course, response to treatment and prognosis (1, 2, 3).

**The association of vitiligo with other endocrine and / or autoimmune diseases**

Adult patients with vitiligo, especially with the generalized form of the disease, are at increased risk of developing a number of endocrine and / or autoimmune diseases, including thyroid disease, T1DM, pernicious anemia, Addison’s disease, rheumatoid arthritis and alopecia areata. Vitiligo can occur before, concurrently or after the occurrence of one or more endocrine and / or autoimmune diseases (1, 3). Epidemiological studies, carried out on a large number of children with vitiligo, showed no increased risk of contracting one of these endocrine and / or autoimmune diseases (10, 29, 30, 31, 32).

Patients with vitiligo most commonly suffer from thyroid disease (30-40%), precisely Hashimoto’s thyroiditis, then hyperthyroidism, hypothyroidism and Graves-Basedow’s disease (1, 33, 34, 35). Unlike adults, children and adolescents with vitiligo demonstrate increased frequency of exclusively Hashimoto’s thyroiditis. Considering the fact that vitiligo usually precedes autoimmune thyroiditis, a possible early diagnosis of the latter is possible. It is therefore recommended that children and adolescents with non-segmental vitiligo undergo annual screening for antibodies against thyreoperoxidase (TPO-Ab), antithyroglobulin antibodies (Tg-Ab) and thyroid-stimulating hormone (TSH) (36, 37, 38).

**Therapy**

Treatment of vitiligo should be initiated with a consultant dermatologist, after presenting therapeutic possibilities and their effectiveness to the patient. The choice of therapeutic options depends primarily on the age and type of vitiligo patients. In all cases it is necessary to use measures to protect against solar radiation and use photoprotective methods (1, 2, 39, 40).

- **Phototherapy.** There are two basic forms of generalized vitiligo phototherapy: PUVA (Psoralen + UVA) photochemotherapy using photosensitive drug (8-methoxypsoralen) in combination with UVA radiation (320-400 nm wavelength) and UVB rays of narrow range of wavelengths of 311 nm (Narrow-band UVB). Targeted laser phototherapy is recommended for focal vitiligo (2, 41, 42).
- **Local corticosteroid therapy:** treatment for at least 3 to 4 months (watch for side effects of corticosteroids!) (7).
- **Other forms of local therapy** (melagenin, calcineurin-inhibitors / pimecrolimus, tacrolimus /, calcipotriol, pseudocatalase) (43, 44, 45)
- **Depigmentation** (monobenzyl hydroquinone ether and 4-methoxy-phenol as a cream) with extensive and generalized vitiligo only in adults and adolescents (2).
– Surgical treatment (epidermal grafting obtained by suction, autologous skin graft method, mini-transplantations) is the method of choice for segmental vitiligo in adults and adolescents (46).
– Cosmetic camouflage methods (47).

The differential diagnosis of vitiligo

The diagnosis of vitiligo is set on the basis of history and the characteristic clinical picture, additional laboratory analysis are rarely needed, skin biopsy even rarer. In children there may be differential diagnostic difficulties in relation to other diseases that are accompanied by hypopigmentation, such as pityriasis alba, pityriasis versicolor varietas alba, post-inflammatory hypopigmentation, piebaldism, morfa, leprosy, tuberous sclerosis, naevus depigmentosus and lichen sclerosus et atrophicus (4, 6). A special difficulty for the recognition of vitiligo arises in fair-skinned people, where it is harder to spot hypopigmentation or depigmentation. A Wood’s lamp (emitting UV rays with wavelengths of 320-400 nm, with a maximum of 365 nm), makes it possible to spot the differences between the complete loss of pigment in vitiligo and various other diseases accompanied by hypopigmentation. Knowing the type of inheritance, the characteristic clinical patterns and symptoms of these diseases is necessary to set an accurate diagnosis of vitiligo (4, 6, 11).

Pityriasis alba

Pityriasis alba (PA) is a common, benign, localized form of hypopigmentation, which is more common in children than in adults. In children under 12 years of age, prevalence is between 1.9% and 5.25% (2, 48).

The etiology and pathogenesis of PA is not clarified. There is a perception that the disease is more common in dark-skinned people. PA is considered a minor form of atopic dermatitis. Recent studies have indicated the frequent occurrence of PA in individuals who sunbathe without using photoprotection, and the onset of PA as a result of frequent sunbathing. In these patients the low levels of serum copper was detected, and it is known that copper plays an important role in the synthesis of tyrosinase, which may explain the hypopigmentation (6, 48).

The clinical pattern shows unclearly bordered hypopigmented maculae and pityriasis-like desquamation on their surface. The disease begins with an erythematous plaque with elevated edges and desquamation occurs after several weeks. Hypopigmentation can last from 6 months to 7 years. The course is prolonged in patients with atopic dermatitis. PA is an asymptomatic disease, although there may be mild itching. The changes are mainly localized on the head, neck and upper limbs. The most common localizations are the head, the forehead and cheekbones, and it rarely occurs in periorbital and perioral regions, unlike vitiligo. There is a generalized form of atypical PA, which is more often seen in adults, and the changes are localized to the thorax (1, 2, 6, 48).

The therapy involves emollients and corticosteroid creams of low and moderate potency, which have limited effectiveness. The use photoprotective creams is recommended. After a few months or years the condition spontaneously withdraws. In the extensive form in adolescents and adults PUVA therapy is applied (48).

Pityriasis versicolor alba varietas

The cause of the disease is Pityrosporum ovale (synonyms: Pityrosporum orbiculare, Malassezia furfur, Malassezia ovalis), part of the normal flora of the skin, which under certain circumstances is transformed from saprophytic yeasts into the mycelal phase and leads to skin diseases. The disease is not contagious and occurs in predisposed peo-
ple, mostly in areas with a humid and warm climate (6, 49).

The clinical picture is presented with café-au-lait or yellowish-brown (versicolor) maculae which are circular, oval or irregular in shape, with unclear edges, up to 1 cm in diameter, with pityriasis-like desquamation at the surface (apparent after mild curettage of the macula) and with a tendency to confluence in plaques. The maculae have characteristic distribution sites, with localization on the chest, back and upper half of the upper arm, and in children they occur on the head and neck. In immunodeficient conditions, the skin changes have atypical distribution (inverse) and the face, creases and some parts of the limbs are affected. The maculae become hypopigmented after sunbathing (Pityriasis versicolor alba varietas) but hypopigmentation is reversible. An asymptomatic infection is the most common, itching is rarely present. If left untreated, the course becomes chronic and could last for years (49).

Diagnosis is made based on the clinical features and the use of a Wood’s lamp, when the yellowish-orange fluorescence of the affected skin is noticed. Native mycological examination with KOH reveals the characteristic appearance of hyphae and spores (“spaghetti and meatballs”) (6, 48, 49).

Local therapy is the method of choice, and imidazole compounds are advised (1% Econazole, Ketoconazole 2%) and ciclopiroxolamine in the form of a solution, spray or cream 1-2 times a day for 2-4 weeks. Selenium sulfide 2.5% shampoo and zinc pyrithione shampoo used once a day (foam should be left on the skin 10 minutes), for two weeks. Residual hypopigmentation lasts a few months after healing, which patients should be warned about. The disease may recur, since Pityrosporum ovale belongs to the normal saprophytic flora of the skin. Systemic therapy is not recommended because Pityrosporum ovale is a normal inhabitant of the skin and cannot be completely removed. For prevention of the disease, a soap is recommended containing Zn and Se sulfide for washing, with mild friction with keratolytics during the summer months as well as the use of a sulfide shampoo with Se and Zn pyrithione, once a week (6, 48, 49).

Piebaldism

Piebaldism is a rare (incidence is 2.5/100000) autosomal dominant disorder caused by the irregular development of melanocytes, which is manifested by the focal absence of melanocytes in the affected skin and hair follicles. The clinical picture is characterized by polyosis and multiple, symmetrical, leukodermic maculae, typically distributed on the sides of the trunk, the anterior abdominal wall and above and below the elbows and knees. Polyosis on the forehead is present in 80-90% of patients. Unlike vitiligo, piebaldism does not appear on the hands, feet and periorificial areas. Hyperpigmented maculae within amelanotic depigmented areas are typical (1, 2, 4).

In patients with piebaldism mutations of C-kit proto-oncogene are found, which encodes the transmembrane receptor and tyrosine kinase activity, causing the omission of migration and differentiation of melanoblasts from the neural tube during embryonic development, in the affected skin areas. Phenotypic characteristics are fully formed at birth and permanent, and usually do not spread afterwards (1, 2). Therapy is symptomatic and includes photoprotection and allows the use of cosmetic camouflage (1, 2).

Tuberous sclerosis

Tuberous sclerosis is an autosomal dominant determined, multisystemic neurocutaneous syndrome, characterized by the formation of multiple hamartomas usually localized in the skin, brain, heart, kidney, liver and lungs. In 2/3 of the patients the disease is the result of sporadic mutations. The char-
acteristic triad consists of deafness, mental retardation and cutaneous angiofibromas, and is seen in only 29% of patients. Early diagnosis is important. At birth or during the first months of life in 97.2% of patients hypopigmented maculae are observed (3 or more), beige-whitish or yellow-whitish in color. They represent a major diagnostic sign. Ash-leaf spots or spear-like and polygonal maculae, sized 0.5 to 2 cm, localized mainly on the trunk or upper legs are characteristic. Less commonly confetti macula or macula of dermatome schedule are seen. Size can vary from 4 mm to 12 cm. Later, chagrin plate, facial angiofibromas, periangual fibromas and plaque on the forehead could emerge. Systemic manifestations of tuberous sclerosis fall within the scope of pediatrics (1, 2, 4, 50).

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