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Vitiligo in Children and Adolescents: a Lliterature Review

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Abstract

Vitiligo is an acquired, often hereditary skin depigmentation disorder, characterized by discrete, well-circumscribed, chalk-white macules or patches. It affects all age groups, but in more than half of the patients it occurs before the age of twenty, when self-image is being formed and social acceptance is of great importance. Although similar to the disease in adults, vitiligo in children and adolescents does have differences in epidemiology, association with other endocrine and/or autoimmune disorders, and treatment. This is a review of vitiligo in the pediatric population, emphasizing key differences with vitiligo in adults. According to the literature reports, we suggest that children and adolescents with vitiligo, especially non-segmental type, should perform annual screening for thyroid dysfunction, particularly for parameters of autoimmune thyroiditis.

Key words

Vitiligo; Child; Adolescent

Vitiligo is an acquired, presumably a hereditary autoimmune skin disorder characterized by progressive, well-circumscribed milky white patches affecting the skin and/or mucosal membranes (1, 2).

Epidemiology

Vitiligo affects individuals of all races worldwide. It is estimated that it affects around 1 – 2% of the world population. Vitiligo is primarily a disease of the young. It affects all age groups, but half of them are under the age of 20 (1 - 8). Epidemiology of childhood vitiligo is similar to that in adults, but there are some specificities of vitiligo in children. Unlike in adults, where it affects both genders equally, childhood vitiligo is more frequent in girls (9). Only 8% of adults with vitiligo have a positive family history, whereas it is positive in 12 – 35% of affected children (5, 7 - 9).

Generalized vitiligo is the most common type, both in children and in adults. It has been reported that from 33% to 78% of children with vitiligo are affected by a generalized type of the disease (4 - 9)

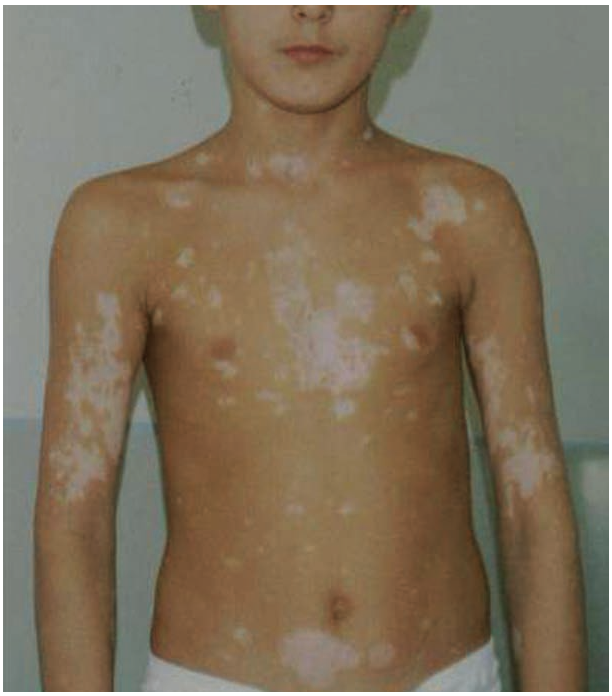

Figure 1. Generalized vitiligo in a 12-year-old boy

(Figure 1). The second most frequent type is focal vitiligo (14.4% - 34.6%). Segmental vitiligo is significantly more frequent in children than in adults. It has a prevalence of 20% in children, but only 5% in adults. Acrofacial (7.6%) and universal vitiligo (0.4%) are rarely found in children (4 - 9).

Etiology and Pathogenesis

The etiology and pathogenesis of vitiligo are not fully understood. It has been known that genetic factors play a certain role in the development of vitiligo (3, 4, 10). In patients with non-segmental vitiligo and positive family history of vitiligo, the disease occurs at a younger age (at the age of 24.8 years on the average), whereas in patients without positive family history it occurs at the age of 42.2 years (11). Recent research shows that there are two possible modes of inheriting vitiligo, both associated with the age of vitiligo development (12). In patients with an early onset of vitiligo (under the age of 30 years), it is caused by dominant mode of inheritance, with incomplete penetration. However, in patients affected by vitiligo after the age of 30, a predisposition to vitiligo is resulting from a recessive genotype and exposure to certain environmental triggers (13, 14). Very early onset of vitiligo (under the age of 7) has also been established in children with a positive family history of vitiligo (15). There is clear evidence that certain HLA haplotypes are strongly associated with positive vitiligo family history, time of onset, severity of the disease, and ethnic background (13, 14). There are several theories of vitiligo pathogenesis: autoimmune, oxidative stress theory, and neurogenic theory (1 - 4).

Autoimmune theory

Autoimmune theory of vitiligo has been best supported by clinical and basic investigations (1, 3, 13 - 15). Some researches show that increased incidence of autoimmune thyroiditis in vitiligo patients is genetically determined. Autoimmune susceptibility locus on chromosome 1 (AIS1) is thought to provoke autoimmune reactions, especially in vitiligo associated with other genes (for example the major histocompatibility complex – MHC, located in the short arm of chromosome 6), and combined with exposure to external or internal factors, it may mediate the development of Hashimoto's thyroiditis (HT) (16, 17). It is common knowledge that genes located on chromosome 17p13 contribute to the development of certain autoimmune diseases: generalized vitiligo, autoimmune thyroiditis, insulin-dependent diabetes mellitus, rheumatoid arthritis, psoriasis, pernicious anemia, systemic lupus erythematosus and Addison's disease. According to recent research of NALP1 protein, it is a gene which plays a major role in the regulation of intracellular innate immunity. DNA sequence variants in the NALP1 region are associated with the increased risk for the development of generalized vitiligo (Figures 2 and 3), and/or other

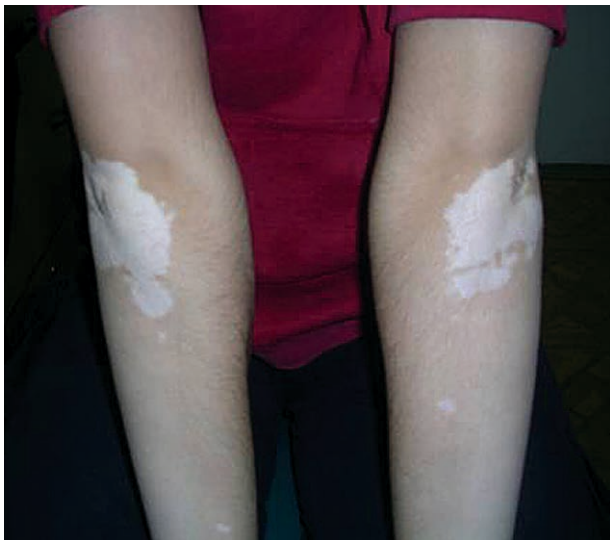

Figure 2. Generalized vitiligo in a 15-year-old girl

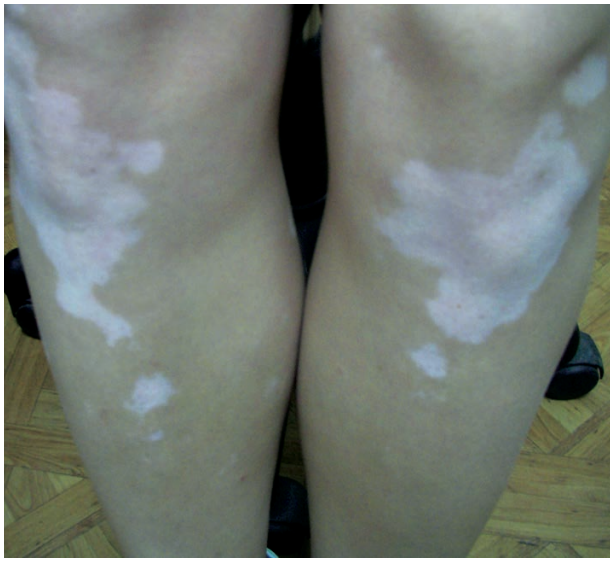

Figure 3. Generalized vitiligo in a 15-year-old girl

associated autoimmune diseases, such as autoimmune thyroiditis (18). It is estimated that autoimmune mechanisms have a key role in the development of non-segmental vitiligo (1 - 3) (Figure 4).

Oxidative stress theory

In the melanocytes of active vitiligo there is an increase of antioxidants, as well as a deficiency of antioxidant enzyme systems, consequently causing oxidative damage in the melanocytes, being the basis of oxidative stress theory (3, 19 - 22).

Neurogenic theory

Development of segmental vitiligo can best be explained by neurogenic theory, which explains lesions to be the result of abnormal release of neurochemical mediators inhibiting melanogenesis, or having toxic effects causing melanocytes destruction (23 - 25). Segmental vitiligo is extremely rarely associated with autoimmune diseases (26, 27) (Figure 5).

Coexistence with endocrine and/or autoimmune diseases

Adult patients with vitiligo are at higher risk for developing a number of endocrine and/or autoimmune diseases, including thyroid gland diseases (mostly Hashimoto's thyroiditis), insulin-dependent diabetes mellitus, pernicious anemia, Addison's disease, autoimmune polyglandular deficiency syndrome, rheumatoid arthritis and alopecia areata. Vitiligo may develop prior, concurrently or after the occurrence of endocrine and/or autoimmune diseases (1, 3, 28). Epidemiological studies, including a large number of children with vitiligo, have not shown an increased risk of above-mentioned diseases (9, 29 - 33). Unlike adults, children and adolescents with non-segmental vitiligo develop more frequently only Hashimoto's thyroiditis (34 - 36) (Figure 6). Given the fact that vitiligo often precedes Hashimoto's thyroiditis, early diagnosis of HT is possible. Therefore, children

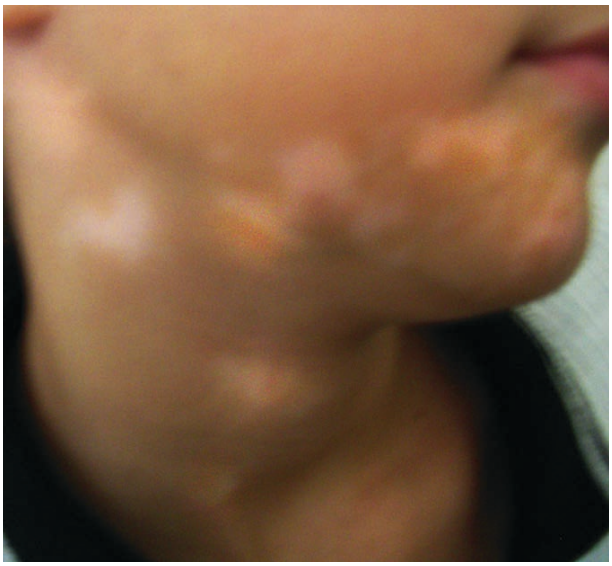

Figure 5. Segmental vitiligo in a 9-year-old girl

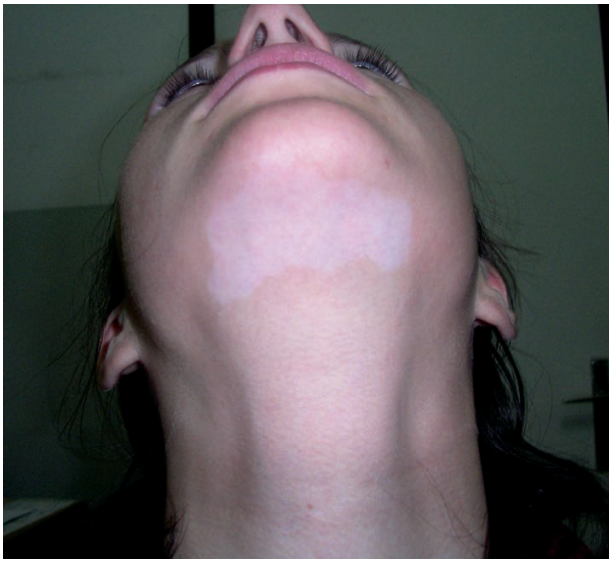

Figure 4. Focal vitiligo in a 17-year-old female patient

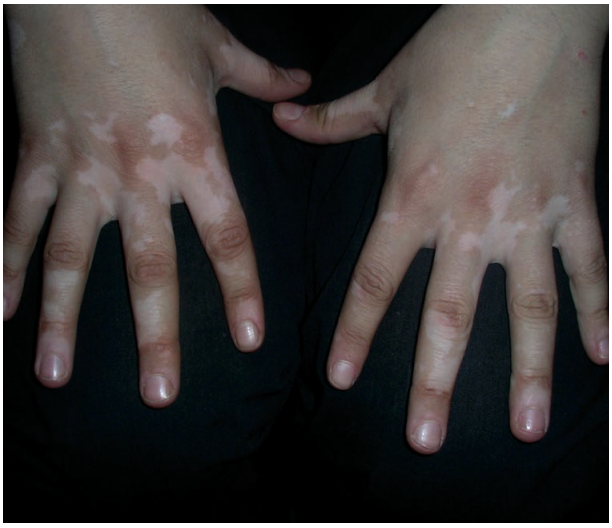

Figure 6. Initial lesions of vitiligo in a 16-year-old adolescent with Hashimoto thyroiditis

and adolescents with non-segmental vitiligo should undergo testing for: thyroid peroxidase antibodies (TPO-Ab), thyroglobulin antibodies (Tg-Ab), and thyroid-stimulating hormone (TSH) once a year (34 - 36).

Differential diagnosis

There may be difficulties in differential diagnosis of childhood vitiligo related to other diseases associated with hypopigmentation such as: pityriasis alba, tinea versicolor alba, postinflammatory hypopigmentation, piebaldism, morphea, leprosy and so on. In order to obtain correct diagnosis of vitiligo, it is necessary to know types of inheritance as well as characteristic signs and symptoms of the above-mentioned diseases (8, 37).

Treatment

Treatment of vitiligo should start with an agreement between the dermatologist and the patient, after treatment options and their efficacy are explained. The treatment option depends on the age of the patient and type of vitiligo (1, 2, 38, 39). Children and adolescents experience the disease differently, depending on their age, locality and severity of lesion distribution, as well as on their personal abilities and reactions of their family and social environment. If the disease has a negative effect on their overall appearance, affecting their self-esteem, they should seek psychological help (40 - 42). All patients suffering from vitiligo should avoid sun exposure and use photoprotection (1, 2).

Phototherapy

Phototherapy includes PUVA (Psoralen + UVA light) therapy, KUVA (Khellin + UVA light) therapy, UVB narrow-band therapy and laser phototherapy (4, 8).

Local PUVA therapy

Local PUVA therapy is recommended for the treatment of non-segmental vitiligo. However, its efficacy is limited to 50 – 60%; recurrences are frequent, as well as adverse effects such as burns and hyperpigmentation (39). This treatment modality is recommended to children with vitiligo affecting less than 20% of body surface, and in whom local therapy has not been successful (5, 6).

Local KUVA therapy

Local KUVA (Khellin + UVA light) therapy exhibits significantly less side effects, while its efficacy is similar (44%) to PUVA therapy (53%) (43).

Systemic PUVA therapy

Systemic PUVA therapy**,** due to its late adverse effects, should be used only in adolescents, particularly in those with 20 – 30% of body surface affected by vitiligo (8). The therapeutic efficacy is rather high (around 70%), but the treatment lasts from 12 to 18 months, twice a week, which requires high motivation and commitment of parents and children (5).

Narrow-band UBV therapy

Narrow-band UBV (311 nm) phototherapy, used both in active and stable generalized vitiligo in adults (efficacy of 63%), has also proven effective in studies including a limited number of children (efficacy of 53%). The cosmetic effects are more acceptable than with PUVA therapy, due to less hyperpigmentation of the surrounding skin (44 - 46). Further investigations concerning its efficacy and possible adverse reactions in children are necessary (8).

Laser therapy

Excimer laser phototherapy (308 nm) has proven successful in localized vitiligo in adults (efficacy of 53%), with less adverse effects in regard to PUVA therapy, but further investigations are needed concerning its safety in children (47, 48).

Local therapy

Corticosteroid therapy

Local corticosteroid therapy has proven efficient in 53% of adults and not more than 64% of children with vitiligo (4, 5, 8). If vitiligo lesions affect the trunk and extremities, local corticosteroid therapy with moderate potency is recommended, whereas low potency corticosteroids are used for facial lesions. The therapy should last at least 3 to 4 months, while better results are obtained in dark-skinned children. Unfortunately, local adverse effects are limiting this mode of treatment in children (4). Segmental vitiligo does not respond to local corticosteroid therapy.

Other local therapy modalities

Other local therapy modalities have limited effects when used as monotherapy, so these agents are mainly used in combination therapy of vitiligo (10). However, they have not been approved for vitiligo therapy by Food and Drug Administration (FDA) in the United States (8).

Melagenine is a human placental extract, which has shown to be effective in the vitiligo therapy in children with lesions affecting the scalp, exhibiting least adverse effects (49).

Calcineurin inhibitors (Pimecrolimus, Tacrolimus) are macrolide immunomodulators which were isolated from *Streptomyces tsukubaensis* in Japan. They are used as an alternative to local corticosteroid therapy, with significantly less adverse effects on sensitive skin regions (face, groin, perigenital region). Successful application of tacrolimus has been reported both in adults and children (efficacy of 41.3%) (50 - 52). Lepe and associates reported that monotherapy using pimecrolimus and tacrolimus showed efficient only in 25% of children with vitiligo (**52**). Tacrolimus has shown good therapeutic results in segmental vitiligo as well (53). According to one study report, tacrolimus caused local hypertrichosis (54). Further investigations on the efficacy and safety of calcineurin inhibitors in the therapy of childhood vitiligo are still necessary (8).

A combination of catalase enzymes and superoxide dismutase, a melon *(Cucumis melo)* extract, decreases the production of hydrogen peroxide by keratinocytes in vitiligo lesions. Topical use of gel containing this extract proved to be successful in 23.5% of vitiligo patients. Combined with narrow-band UVB phototherapy, repigmentation was achieved in 35.5% of patients with vitiligo, without any reported side effects (55).

Calcipotriol is a vitamin D analogue which induces melanogenesis through an unknown mechanism involving melanocytes 1-alpha-25 dihydroxy vitamin D3 receptors. It has been successfully used in the therapy of childhood vitiligo. Its most common side effect is local irritation (56). In a study including 18 children with vitiligo, complete repigmentation was reported in 10 (56%) after local application of calcipotriol (57). Significantly better results were achieved when it was combined with local corticosteroids (58).

Surgical therapy

Surgical therapy is indicated as a therapy of choice for patients with segmental vitiligo, but only in adolescents and adults (1, 2, 3, 10). The most common procedures include: ***epidermal grafting using the tops of suction, autologous skin grafting, and miniature punch grafting*** (1 - 3). *Autologous* ***skin*** *grafting* is popular in the management of focal and stable generalized vitiligo with an efficacy of 87% and 95%, respectively (38). This procedure is highly complicated and requires general anesthesia. Treatment results are better in the young, especially when combined with PUVA therapy, so it is recommended to adolescents with segmental vitiligo (8). Gupta and Kumar were successful in the treatment of vitiligo in adolescents, using *epidermal grafting and tops of suction*, combined with postsurgical phototherapy (59). Other surgical procedures, such as tattooing vitiligo lesions, are recommended only in focal vitiligo (60).

Depigmentation

Depigmentation of the remaining pigmented skin islands using monobenzyl ether of hydroquinone and 4-methoxyphenol cream is indicated only in adult patients with extensive vitiligo (loss of pigment over 40% of body surface), and universal vitiligo (1 - 4, 7, 8).

Cosmetic camouflage

Cosmetic camouflage products are inexpensive, easy to use and have no adverse effects (61). However, their use in children is limited, because most of these products are not water-proof and may be removed during play. On the other hand, some resistant products give no acceptable match for the surrounding, normally pigmented skin (5).

Conclusion

Vitiligo causes significant psychological and emotional distress in children and adolescents (5, 40 - 42). We can conclude that there are important differences in the epidemiology, comorbidity with other diseases, and therapy of vitiligo in children and adults. Results of recent research of vitiligo in children and adolescents point to the necessity of screening for thyroid dysfunction, especially for autoimmune thyroiditis (34 - 36). Phototherapy and local use of corticosteroids,

most commonly used in the management of vitiligo in adults, are less successful in children (8). Further clinical investigations are necessary to find efficient therapeutic procedures adjusted to the treatment of childhood vitiligo (8).

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Abbreviations

AIS - autoimmune susceptibility
FDA- Food and Drug Administration
HT - Hashimoto's thyroiditis
KUVA- khellin + UVA therapy
PUVA - psoralen + UVA
Tg-Ab - thyroglobulin antibodies
TPO –Ab – thyroid peroxidase antibodies
TSH - thyroid-stimulating hormone

Vitiligo kod dece i omladine - pregled literature

Sažetak

Uvod: Vitiligo je stečeno oboljenje, najverovatnije autoimune prirode, ponekad sa jasnom naslednom komponentom, koje se karakteriše progresivnim, jasno ograničenim, mlečnobelim mrljama na koži i/ili sluzokožama (1,2).
Epidemiologija: Vitiligo je prvenstveno bolest mladih, kod polovine svih obolelih javlja se pre 20 godine života. Epidemiologija vitiliga kod dece je slična kao kod odraslih sa vitiligom, ali za razliku od odraslih sa vitiligom, gde je učestalost javljanja kod oba pola približno ista, kod dece se vitiligo češće javlja kod devojčica. U porodičnoj anamnezi

obolele srodnike ima 12 do 35% obolele dece, za razliku od oko 8% odraslih bolesnika sa vitiligom.
Generalizovani vitiligo je najčešći tip vitiliga i kod dece i kod odraslih. Navodi se da 33% do 78% dece sa vitiligom ima generalizovani oblik bolesti, 14,4% do 34,6% ima fokalni vitiligo dok se segmentni vitiligo značajno češće javlja kod dece nego kod odraslih. Prevalenca segmentnog vitiliga kod dece iznosi oko 20%, a kod odraslih svega 5%. Akrofacijalni (7,6%) i univerzalni vitiligo (0,4%) se ređe viđaju kod dece.
Etiologija i patogeneza: Poznato je da genetski faktori imaju izvesnu ulogu u nastanku vitiliga. Kod bolesnika sa ranim početkom vitiliga (pre 30 godine), vitiligo je uslovljen dominantnim načinom nasleđivanja, sa nekompletnom penetracijom. Međutim, kod bolesnika sa kasnim početkom vitiliga (posle 30 godine), predispozicija za vitiligo je rezultat recesivnog genotipa i uticaja spoljašnje okoline. Raniji početak vitiliga (do 7 godine) utvrđen je i kod dece sa vitiligom i pozitivnom porodičnom anamnezom za vitiligo.
Kao moguće teorije patogeneze vitiliga navode se: autoimuna, teorija oksidativnog stresa i neurogena teorija. Autoimuna teorija ima najčvršću podlogu u kliničkim i bazičnim istraživanjima. Neka istraživanja pokazuju da je povećana učestalost autoimunog tireoiditisa kod pacijenata sa vitiligom genetski determinisana. Lokus AIS1 (eng. ***a***uto***i***mmune ***s***usceptibility) na hromozomu 1, odgovoran je za sklonost ka autoimunom reagovanju, naročito za vitiligo, a uz sadejstvo različitih spoljašnjih ili unutrašnjih faktora, može posredovati u nastanku Hashimoto tireoiditisa. Poznato je takođe da geni na hromozomu 17p13 doprinose nastanku određenih automunih bolesti npr.generalizovanog vitiliga i autoimunog tireoiditisa. Novija istraživanja opisuju NALP1 protein, kao produkt gena koji reguliše intaktnost imunog sistema. Promene u nizu DNA u oblasti NALP1, udružene su sa povećanim rizikom za nastanak generalizovanog vitiliga i/ili drugih združenih autoimunih bolesti, kao što je autoimuni tireoiditis. Smatra se da autoimuni mehanizmi imaju ključnu ulogu za nastanak nesegmentnog vitiliga. U melanocitima aktivnog vitiliga ustanovljeno je povećanje oksidanata kao i deficit antioksidantnih enzimskih sistema, sa posledičnim oksidativnim oštećenjem melanocita, na čemu se bazira teorija oksidativnog stresa. Nastanak segmentnog vitiliga najbolje se može objasniti neurogenom teorijom, prema kojoj se iz nervnih završetaka oslobađaju neurohemijski medijatori, koji inhibišu melanogenezu ili imaju toksično dejstvo na melanocite uništavajući ih. Segmentni vitiligo je izuzetno retko udružen sa autoimunim bolestima.
Udruženost sa endokrinim i/ili autoimunim oboljenjima: Vitiligo se može javiti pre, istovremeno ili posle nastanka endokrinih i/ili autoimunih bolesti. Epidemiološke studije, rađene na velikom broju dece sa vitiligom, nisu pokazale povećan rizik oboljevanja od navedenih oboljenja. Za razliku od odraslih, kod dece i adolescenata sa nesegmentnim vitiligom dokazana je povećana učestalost isključivo Hashimoto tireoiditisa. S obzirom da vitiligo najčešće prethodi pojavi tireoiditisa, predlaže se da se kod dece i adolescenata sa nesegmentnim vitiligom jednom godišnje uradi skrining na tireoperoksidazna, tireoglobulinska antitela i tireostimulišući hormon.
Diferencijalna dijagnoza: Kod dece mogu postojati diferencijalno dijagnostičke poteškoće u odnosu na druge bolesti koje su praćene hipopigmentacijom, kao što su: pityriasis alba, tinea versicolor varietas alba, postinflamatorne hipopigmentacije, pijebaldizam, morfea, lepra i druge.
Terapija: Izbor terapijske opcije zavisi od uzrasta bolesnika i tipa vitiliga. Kod svih obolelih od vitiliga neophodna je primena mera zaštite od sunčevog zračenja i korišćenje fotoprotektivnih sredstava.
Lokalna primena PUVA (psoralen + UVA zraci) terapije se preporučuje za lečenje nesegmentnog vitiliga, ali je efikasnost ograničena na 50-60% i česti su recidivi vitiliga, kao i neželjeni efekti u vidu opekotina i hiperpigmentacija. Ovaj vid terapije se preporučuje kod dece kod koje vitiligo zahvata manje od 20% površine tela i kod kojih nije bila uspešna lokalna terapija.

Lokalna primena KUVA terapije (khellin + UVA zraci) ima znatno manje neželjenih efekata, a efikasnost je slična (44%) kao kod sistemske PUVA terapije (53%).

Sistemska primena PUVA terapije je zbog svojih kasnih neželjenih efekata ograničena na uzrast adolescenata kod kojih vitiligo zahvata više od 20-30% površine tela. Terapijska efikasnost je visoka (oko 71%), ali lečenje traje 12 do 18 meseci, dva puta nedeljno.

Fototerapija UVB zracima uskog spektra (311 nm), koja se primenjuje kod aktivnog ali i stabilnog generalizovanog vitiliga kod odraslih (efikasnost 63%), se pokazala uspešnom (efikasnost 53%) i u studijama sa ograničenim brojem dece. Kozmetski efekat je bolji nego kod PUVA terapije, jer je manje izražena hiperpigmentacija okolne kože.

Fokusirana laserska fototerapija (308 nm) se pokazala uspešnom kod lokalizovanog vitiliga u odraslih (efikasnost 53%), sa manje neželjenih efekata od PUVA terapije, ali su neophodna dalja ispitivanja o bezbednosti primene kod dece.

Lokalna kortikosteroidna terapija se pokazala uspešnom kod 53% odraslih i najviše 64% dece sa vitiligom. Lečenje treba sprovoditi najmanje 3 do 4 meseca, a bolji rezultati se postižu u tamnoputе dece. Segmentni vitiligo ne raeguje na lokalnu terapiju kortikosteroidima.

Drugi vidovi lokalne terapije imaju ograničeno dejstvo kao monoterapija, pa se navedeni lekovi uglavnom koriste u kombinovanoj terapiji vitiliga. Međutim, oni nisu prihvaćeni za terapiju vitiliga, od strane FDA (engl. *Food and Drug Administration*) u USA: melagenin koji predstavlja ekstrakt humane placente, se pokazao uspešnim u terapiji vitiliga poglavine kod dece, uz minimalne neželjene efekte; kalcineurin inhibitori (pimekrolimus, takrolimus) se mogu koristiti u područjima osetlijve kože (lice, prepone, perigenitalna regija). Uspešna primena takrolimusa je opisana i u odraslih i u dece (efikasnost do 41,3%), kao i u lečenju segmentnog vitiliga. Može se razviti lokalna hipertrihoza na mestu aplikacije takrolimusa; kombinacija enzima katalaze i superoksid dizmutaze ekstraktovanih iz posebne vrste dinje *(Cucumis melo),* smanjuje proizvodnju hidrogen peroksida od strane keratinocita u lezijama vitiliga. Opisana je uspešna lokalna primena ovog ekstrakta, u obliku gela, u 23,5% obolelih od vitiliga, u kombinaciji sa UVB zracima uskog spektra, repigmentacija je postignuta u 35,3% pacijenata sa vitiligom, pri čemu nisu zabeleženi neželjeni efekti; kalcipotriol stimuliše melanogenezu nepoznatim mehanizmom delujući na 1- alfa- 25 dihidroksi- vitamin D3 receptore melanocita. Sa uspehom (kompletnu repigmentaciju u 56%) je korišćen u terapiji vitiliga kod dece, a kao neželjeni efekat se navodi lokalna iritacija. Znatno bolji rezultati su postignuti u kombinaciji sa lokalnom primenom kortikosteroida.

Hirurško lečenje je terapija izbora za segmentni vitiligo ali isključivo kod adolescenata i odraslih osoba. Najznačajnije metode su: presađivanje epiderma dobijenog sukcijom, metoda autolognog kožnog grafta, i metoda minitransplantacije *punch* biopsijama. Metoda autolognog kožnog grafta se pokazala uspešnom kod fokalnog i stabilnog generalizovanog vitiliga. Efikasnost je između 87% i 95%. Postupak je veoma komplikovan i podrazumeva opštu anesteziju. Uspešnije je kod mlađih, naročito u kombinaciji sa PUVA terapijom, pa se savetuje adolescentima sa segmentnim vitiligom. Opisani slučajevi uspešnog lečenja vitiliga kod adolescenata, metodom presađivanja epiderma dobijenog sukcijom, uz naknadnu fototerapiju. Primena tetovaže vitiligo lezija, se preporučuju samo kod fokalnog vitiliga.

Depigmentacija malobrojnih, preostalih pigmentovanih delova kože, upotrebom monobenzil etar hidrokvinona i 4-metoksi-fenola u vidu krema, primenjuje kod ekstenzivnog (gde vitiligo zahvata više od 40% površine tela) i univerzalnog vitiliga i to isključivo kod odraslih osoba.

Kozmetička kamuflažna sredstva su relativno jeftina, laka za upotrebu i nemaju neželjenih efekata. Njihova upotreba kod dece je ograničena stoga što većina ovih preparata nije vodootporna i lako se mogu skinuti tokom dečje igre.

Zaključak**:** Možemo zaključiti da postoje značajne

razlike u epidemiologiji, udruženosti sa drugim oboljenjima i terapiji vitiliga kod dece i odraslih. Rezultati najnovijih istraživanja vitiliga kod dece i adolescenata ukazuju na potrebu skrininga na tireoidnu disfunkciju, posebno na autoimuni tireoiditis. Fototerapija i lokalna primena kortikosteroida, predstavljaju terapijske modalitete koji se najčešće koriste u lečenju vitiliga kod odraslih, ali se njihova primena pokazala manje uspešnom u lečenju vitiliga kod dece.

Ključne reči

Vitiligo; deca; adolescenti