PERIORAL DERMATITIS: STILL A THERAPEUTIC CHALLENGE

Zrinka Bukvić Mokos[1], Ana Kummer[2], Elvira Lazić Mosler[3], Romana Čeović[1] and Aleksandra Basta-Juzbašić[1]

[1]University Department of Dermatology and Venereology, Zagreb University Hospital Center, School of Medicine, University of Zagreb, Zagreb; [2]Blaženka Tomić-Kummer Pediatric Office, Zaprešić; [3]Dr. Ivo Pedišić General Hospital, Sisak, Croatia

SUMMARY – Perioral dermatitis is a common and often chronic dermatosis. In its classic form, it primarily affects women aged 15 to 45 years, but there are also variants including lupus-like and granulomatous perioral dermatitis, where granulomatous form is more common in childhood and affects mostly prepubescent boys. The etiopathogenesis of the disease remains unclear, but there is a frequent finding of prolonged use of topical products, especially corticosteroids, in the treatment of rosacea and seborrheic dermatitis, preceding the clinical manifestation of perioral dermatitis. Other causes important for the occurrence of the disease include various skin irritants, as well as other physical and hormonal factors, which all share the epidermal barrier dysfunction as an underlying main pathogenic factor. Clinical presentation of papulovesicular eruption in the perioral region with a typical narrow spared zone around the edge of the lips is characteristic. Therapeutic approach should be individually addressed, depending on the severity of clinical presentation and patient's age, with special attention to patient's education and continuous psychological support. In mild forms of perioral dermatitis, 'zero therapy' is the treatment of choice. In the initial treatment period, patients with steroid-induced perioral dermatitis should be closely followed up because the rebound phenomenon usually develops after cessation of previous topical treatment. In moderate disease, treatment includes topical metronidazole, erythromycin, and pimecrolimus, whereas in more severe cases the best validated choice is oral tetracycline in a subantimicrobial dose until complete remission is achieved. Systemic isotretinoin should be considered as a therapeutic option for patients refractory to all standard therapies.

Key words: *Dermatitis, perioral – etiology; Dermatitis, perioral – therapy; Individualized medicine*

Introduction

Perioral dermatitis is a dermatosis with subacute or chronic course, first described in 1957 by Frumess and Lewis under the term "light-sensitive seborrhoeid"[1]. It manifests with papules, papulovesicles and papulopustules with a diameter of 1 to 2 millimeters, which progressively join to clusters, situated on erythematous base. Skin changes typically appear in the perioral region with a characteristic spared skin zone around the edge of lips. Lesions gradually spread to nasolabial folds, cheeks and lateral portions of lower lids.

Light-skinned people are primarily affected; predominantly women aged 15 to 45 years, with a peak incidence in the second and third decade of life. Besides, the number of male patients suffering from perioral dermatitis has also been increasing, presumably because of the more common use of cosmetic products among men. Perioral dermatitis may also occur in childhood and it affects mostly boys, with the peak incidence in the prepubescent period[2].

Correspondence to: *Assist. Prof. Zrinka Bukvić Mokos, MD, PhD*, University Department of Dermatology and Venereology, Zagreb University Hospital Center, Šalata 4, HR-10000 Zagreb, Croatia
E-mail: zrinka.bukvic@zg.t-com.hr

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Etiopathogenesis

In a large portion of patients with perioral dermatitis, there is an evident history of previous use of topical corticosteroids. On the other hand, it can occur without previous topical corticosteroid use (idiopathic perioral dermatitis). Some authors suggest that perioral dermatitis is a result of facial skin intolerance to repetitive irritation[3]. It is believed that the main pathogenic factor is impaired skin barrier function. Additionally, the majority of patients have atopic diathesis[4]. Although the exact etiopathogenesis of perioral dermatitis has not yet been fully explained, several etiopathologic factors have been proposed.

Topical corticosteroids

The absorption level of topical corticosteroids depends on the potency of corticosteroids, the body area (face and neck absorb greater amounts of corticosteroids) and the duration of administration[5].

The duration of topical steroid use required to induce perioral dermatitis varies among individuals; by own experience, only a few weeks of application of even mid-strength or mild topical steroid can result in typical perioral dermatitis, whereas in some patients it develops after years of topical steroid application. The reason for uncritical use of corticosteroids varies among patients, but, according to our experience, the most common primary dermatoses include seborrheic dermatitis and rosacea. During a period of 3 years (1999-2001), in our Department we followed 450 patients with a history of prior use of topical steroids lasting from several weeks to even 24 years. The primary dermatosis was seborrheic dermatitis in 203 (45.1%), rosacea in 158 (35.1%), acne in 44 (9.8%), unrecognized dermatomycosis in 8 (1.8%) patients, and other reasons like cosmetic cleansing or after-shave use in 37 (8.2%) patients. The common scenario includes a patient who starts application of a less potent corticosteroid with transient improvement of the initial skin lesions, but later on it is followed by development of full perioral dermatitis manifestation. This often leads to further use of high-potent corticosteroids in order to alleviate skin symptoms, which only makes clinical presentation ever more severe, leading to the vicious circle of steroid usage and gradual worsening of the disease.

There are several epidermal and dermal changes that have been associated with the prolonged use of topical steroids. Generally, patients with perioral dermatitis have an initially impaired epidermal barrier function, with topical steroids only aggravating this disturbance[6]. Consequently, transepidermal water loss (TEWL) is increased, accompanied by delayed response and recovery of permeability barrier. The amount of epidermal lipids including ceramides is reduced, whereas dermal changes include reduction of collagen and elastic fibers. It is believed that topical corticosteroids damage the wall of the hair follicle, which is followed by edema in the follicle cells, which may play the crucial role in the development of granulomatous perioral dermatitis[7,8].

Skin irritants

Excessive use of moisturizing creams, especially the ones based on petroleum jelly or paraffin, can cause follicular occlusion and irritation. As a result, epithelial barrier becomes dysfunctional, leading to edema of the *stratum corneum* and increased TEWL[9]. This manifests as a feeling of tension and dryness of the skin. Other skin irritants, such as decorative cosmetics, creams with a high sun protecting factor, or even fluorinated toothpaste can lead to the same skin disorders and manifestation of perioral dermatitis.

Physical factors

Sunlight and exposure to ultraviolet radiation could be a possible cofactor in the development of perioral dermatitis. On the other hand, some patients noted skin changes getting worse during winter and prolonged wind exposure.

Hormonal factors

Since the majority of people suffering from perioral dermatitis are women, hormonal changes and the use of oral contraceptives are considered to be the possible etiologic factors. Some women noted worsening of skin changes during premenstrual period[2].

Microbiological factors

Although the bond between the microbiological factors and perioral dermatitis has not yet been definitely proven, there have been cases in which certain

species, such as *Candida albicans*, fusiform bacteria and *Demodex folliculorum* mite were isolated from skin lesions.

Clinical Presentation

Classic perioral dermatitis

Perioral dermatitis typically presents with numerous small, red to red-brown papules, papulovesicles and rarely papulopustules, 1 to 2 millimeter in diameter. Lesions are situated on a sharply delimited erythematous base and appear mostly in the perioral region, with a characteristic spared zone around the edge of lips. Skin lesions are often grouped together and they can fuse and affect larger areas, appearing on the nasolabial folds and lower eyelids. Wider areas of the face, such as the glabella, upper eyelids and the forehead are rarely affected.

Diffuse erythematous skin shows signs of discrete scaling, whereas the surrounding skin is often dry, leading to sensation of tension, slight burning and pain in the affected areas. Secondary bacterial infection of the skin lesions or infestation by *Demodex* mites is also possible in patients with chronic perioral dermatitis.

Differential diagnosis includes rosacea, seborrheic dermatitis, childhood granulomatous perioral dermatitis, allergic contact dermatitis and 'lip-licking' cheilitis.

Lupus-like perioral dermatitis

Lupus-like perioral dermatitis is a clinical variant of perioral dermatitis. The main difference from the classic form is the appearance of dense clusters of larger, succulent, red to brown papules and papulosquamous lesions in the perioral area. Periorbital region can be affected as well. Skin lesions show yellowish discoloration on diascopy and are more prone to heal with scars[10].

Childhood granulomatous perioral dermatitis

Granulomatous perioral dermatitis is a form of perioral dermatitis which is more common in children. First described by Gianotti *et al.* in 1970[11], it was thought to be almost exclusive among Afro-Caribbean children, which gave its first name, 'facial Afro-Caribbean childhood eruption'. But this clinical entity got its current name in 1996, implying that it manifests in childhood, regardless of race[12,13].

It occurs in children aged 7 months to 14 years, mainly in prepubescent period and is more common in boys[14]. Topical steroids (particularly fluorinated corticosteroids) are considered as either the main cause or as a worsening factor. Clinical presentation includes discrete yellow to brown or even reddish papules 1 to 3 millimeter in diameter, positioned primarily in the perioral region. Skin changes can also be found in the perinasal and periocular areas, as well as in the extrafacial areas, such as limbs or trunk. The course of disease is mild and skin lesions heal without scarring and pigmentation disorders. Skin changes regress spontaneously after a few months and therefore most cases require no therapy.

Differential diagnosis includes several skin conditions such as classic perioral dermatitis, granulomatous rosacea, sarcoidosis, and disseminated miliary lupus of the face.

Therapy

The choice of treatment depends on the severity of the disease and patient's compliance. Mild forms of perioral dermatitis can be successfully treated with topical agents, whereas moderate to severe forms of the disease require systemic therapy.

However, the first therapeutic step should consist of complete cessation of all topical products, which is called 'zero therapy' and it is usually applied during the first few weeks of treatment. During this period, the application of all topical products, including both skin care products and topical medications, should be discontinued, particularly topical corticosteroids and lipid-rich cosmetics. The patient should also be instructed to avoid all skin care products, soaps, astringents and abrasives. According to our experience, local application of compresses of normal saline solution or chamomile tea during the few initial weeks of treatment is usually beneficial.

'Zero therapy' may be sufficient in the treatment of mild forms of perioral dermatitis. On the other hand, special attention should be paid to patients with corticosteroid-induced perioral dermatitis, who usually develop 'rebound phenomenon' after cessation of topical steroids, manifested with edema, erythema and papu-

lopustular eruption with itching and burning. At this point, there is a high risk of patient's non-compliance, when some patients continue to apply the same or another topical steroid. However, some authors suggest tapering the frequency of topical steroid application or prescribing lower potency topical steroid, with the aim to mitigate the rebound flare. This approach is not consistent with our experience, as we suggest abrupt cessation of topical steroids, since 'tapering' approach commonly leads only to further uncontrolled use of steroids and prolongs the treatment. Patients should be explained that during the first few weeks, exacerbations are expected and that the treatment can take a long course in severe cases. Therefore, continuous psychological support and encouragement is essential for good compliance and therapeutic success.

Topical therapy

Several topical agents have been successfully used in the treatment of perioral dermatitis, but no single topical medication has shown to be superior to others. Topical medications are required when 'zero therapy' applied for a few weeks produced no appropriate effect and are usually sufficient in moderate forms of the disease. However, some patients complain of irritation after introducing any topical agent, which is most commonly observed in corticosteroid-induced perioral dermatitis. In these patients, the period of 'zero therapy' should be prolonged.

Among topical agents, metronidazole is most commonly used in the treatment of perioral dermatitis. It is a synthetic derivative of nitroimidazole with antimicrobial, anti-inflammatory and antioxidant properties[15,16]. A retrospective study performed by Nguyen and Eichenfeld included 79 children and adolescents with perioral dermatitis[17]. Treatment with metronidazole cream or gel was associated with clearing of the rash, whereas treatment with a calcineurin inhibitor, hydrocortisone, sulfacetamide, or an antifungal agent was not effective. The authors conclude that topical metronidazole for 1 to 2 months should be the first line treatment in children with perioral dermatitis, with the addition of oral erythromycin if the condition persists. On the other hand, in a prospective study that included 108 adult patients with perioral dermatitis, 1% topical metronidazole was compared with oral tetracyclines. Treatment lasted for 8 weeks and the results revealed that metronidazole led to reduction of the number of papules, but tetracyclines obtained better results, leading to complete regression of the rash[15]. However, topical metronidazole is proven to be a good therapeutic choice in cases when tetracyclines are contraindicated or when patients refuse systemic treatment[16].

Other topical agents that have been used in the treatment of perioral dermatitis include topical erythromycin, azelaic acid, adapalene, and calcineurin inhibitors[18]. Topical erythromycin was compared with oral doxycycline and placebo in a study that included 99 patients; 33 patients were treated with topical erythromycin, 35 patients were treated with perioral doxycycline, and 31 patients received placebo. In both patient groups, treated with either topical erythromycin or perioral tetracycline, significantly better therapeutic effects were observed when compared to the group that received placebo. Also, there was no difference in the effectiveness between topical erythromycin and perioral doxycycline[19].

Azelaic acid has also been successfully used in patients with perioral dermatitis[20]. Its use has been particularly investigated in children with perioral dermatitis. Jansen *et al.* report good therapeutic results with 20% azelaic acid cream when treated 8 children with perioral dermatitis, aged 3 to 12 years. Complete remission was observed within 4 to 8 weeks of cream administration[21].

Therapeutic effect of pimecrolimus, a topical calcineurin inhibitor, was investigated in a study conducted on 40 patients aged 21 to 69 years; 1% pimecrolimus cream was administered twice a day for 4 weeks, with 50% reduction of the severity index after 2 weeks of treatment[22]. However, topical calcineurin inhibitors should be used with caution, as there are reports of induction of rosaceiform dermatitis after the use of tacrolimus ointment. The authors have suggested the possible role of various factors in the development of this phenomenon, including occlusive properties of the ointment, as well as proliferation of *Demodex* due to local immunosuppression and vasoactive properties of tacrolimus[23].

Systemic therapy

Systemic treatment is the treatment of choice in severe cases of perioral dermatitis and in mild to mod-

erate forms of the disease if there is no clinical improvement after topical therapy.

Oral tetracyclines are systemic treatment of choice in patients with perioral dermatitis, except for children younger than 8 years, pregnant women, and in cases of hypersensitivity to tetracyclines. In this indication, therapeutic effect of tetracyclines lies in their anti-inflammatory activity, including inhibition of nitric oxide production, down-regulation of matrix metalloproteinase expression, inhibition of serin protease activity, and reduction in the activity of reactive oxygen species. First generation tetracyclines were gradually replaced by doxycycline and minocycline. Nowadays, doxycycline is favored, given that minocycline may induce autoimmune hepatitis and systemic lupus erythematosus-like syndrome. Traditionally, doxycycline has been administered in the initial dose of 100 to 200 mg daily; the dose is halved after 3 to 4 weeks and continued to complete regression of clinical symptoms. Treatment period usually took 8 to 10 weeks. However, the fact that there is no definitive evidence that perioral dermatitis is caused by bacteria has led the authors to administer subantimicrobial dose of doxycycline (modified release, 40 mg daily). Therapeutic effect of this dose on inflammatory lesions was equal when compared with doxycycline 100 mg daily, with advantages of the subantimicrobial dose in the absence of antibiotic resistance and a significantly lower risk of gastrointestinal side effects[24].

Oral macrolides are a therapeutic option in cases when tetracyclines are contraindicated. The macrolide of choice is erythromycin, which has shown effectiveness particularly in treating children with granulomatous perioral dermatitis[12].

Isotretinoin is used in rare cases of perioral dermatitis that have been refractory to any other therapeutic option. Good therapeutic results were obtained in lupus-like perioral dermatitis and in childhood granulomatous perioral dermatitis[10,25].

Discussion

Treatment algorithm for perioral dermatitis has been proposed and it serves as a general and useful guideline[3]. However, there is no universal therapeutic approach applicable to all patients. The choice of treatment primarily depends on the severity of the disease, but also on various factors including facial skin tolerance, patient's compliance and the results of previous therapy. The initial treatment period is of particular importance in patients with steroid-induced perioral dermatitis because the rebound phenomenon usually develops after cessation of previous topical treatment. If the patient is not properly educated, the compliance is poor and the patient usually stops with recommended treatment and continues with the application of even more potent topical steroids. Another delicate issue is the choice of time when to stop with 'zero therapy' and introduce topical medication. As topical steroids aggravate disruption of the epidermal barrier, some patients with steroid-induced perioral dermatitis often do not tolerate any topical product for several weeks and experience burning sensations even after application of neutral creams. Furthermore, when choosing the topical treatment option, the risk of irritation should be considered, particularly when administering topical retinoids and azelaic acid. Both exacerbation of the disease in the initial period and poor tolerance of topical agent may again influence patient compliance. Additionally, some patients with mild and moderate disease cannot accept that in some cases therapeutic effect of topical treatment can be observed only after several weeks and therefore interrupt the treatment. In such cases, earlier introduction of systemic therapy should be considered. On the other hand, some patients refuse oral tetracyclines and prefer topical treatment even in severe cases.

Further issue that should be carefully considered is the duration of treatment with oral tetracyclines. The treatment should be continued until complete remission is achieved, which is usually observed after 8-10 weeks of treatment. It has been observed that recurrences are more likely to develop if the duration of systemic treatment is not sufficient[26]. As there is evidence for increasing development of antibiotic-resistant bacterial strains, long term treatment with doxycycline 100 mg daily should be avoided. The absence of the risk of antibiotic resistance and a significantly lower risk of gastrointestinal side effects favor the use of subantimicrobial dose of doxycycline (modified release, 40 mg daily). Finally, there are rare but not negligible patients who are refractory to all standard therapeutic options. In these patients, treatment with low doses of isotretinoin should be considered, with

special attention to women of childbearing potential because of its teratogenic effect, who then require adequate contraception.

It is concluded that therapeutic strategy for perioral dermatitis should be adjusted individually, with special attention to patient education and continuous psychological support.

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Sažetak

PERIORALNI DERMATITIS: JOŠ UVIJEK TERAPIJSKI IZAZOV

Z. Bukvić Mokos, A. Kummer, E. Lazić Mosler, R. Čeović i *A. Basta-Juzbašić*

Perioralni dermatitis je česta dermatoza, nerijetko kroničnog tijeka, od koje najčešće obolijevaju žene u dobi od 15 do 45 godina. Uz klasični oblik perioralnog dermatitisa postoje još i lupoidni te granulomatozni oblik bolesti koji se najčešće javlja u dječaka u predpubertetskom razdoblju. Etiopatogeneza perioralnog dermatitisa nije u potpunosti razjašnjena, no zna se da važnu ulogu ima dugotrajna uporaba lokalnih pripravaka od kojih su najvažniji lokalni kortikosteroidi. Uz to, za nastanak bolesti važni su i razni kožni iritansi te drugi fizikalni i hormonski čimbenici koji narušavaju funkciju epidermalne barijere, poremećaj koje je osnovni patogenetski čimbenik perioralnog dermatitisa. Klinička slika je znakovita: nalazi se papulovezikulozna erupcija s tipičnom uskom pošteđenom zonom oko ruba usnica, koja je temelj za postavljanje dijagnoze bolesti. U terapiji je nužan individualni pristup koji ovisi o težini kliničke slike i dobi bolesnika, s naglaskom na podučavanju bolesnika i stalnoj psihološkoj potpori. Takozvana „nulta terapija" je najbolji pristup u slučaju blažih oblika bolesti, pri čemu u početnom razdoblju liječenja osobitu pozornost zahtijevaju bolesnici s perioralnim dermatitisom izazvanim steroidima, s obzirom na to da se u tom razdoblju očekuje pogoršanje znakova i simptoma bolesti uzrokovano naglim prestankom primjene dotadašnjih topikalnih pripravaka. Za liječenje umjereno teških oblika bolesti dolaze u obzir lokalni metronidazol, eritromicin i pimekrolimus, dok su oralni tetraciklini lijek izbora u težim slučajevima perioralnog dermatitisa, a primjenjuju se u subantimikrobnoj dozi do potpunog povlačenja promjena na koži. Sustavno liječenje izotretinoinom je terapijski izbor u bolesnika refraktornih na sve druge standardne oblike liječenja.

Ključne riječi: *Dermatitis, perioralni – etiologija; Dermatitis, perioralni – terapija; Individualizirana medicina*