

## DIFFERENTIAL DIAGNOSTICS OF PAINFUL CONDITIONS OF ORAL MUCOSA

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### Summary

Orofacial pain is a common complaint and challenging diagnostic problem. Among numerous causes of orofacial pain, the most common are diseases of teeth and periodontium, followed by various diseases and lesions of the oral mucosa. Pain of the oral mucosa is an accompanying symptom of different mucosal lesions caused by local or systematic factors. This type of pain belongs to the category of superficial somatic pain, termed mucogingival pain. However, the pain of oral mucosa may be present in the absence of pathological findings. This type of pain may be caused by lesion of the nervous system, and is termed neuropathic pain, or it may be result of psychogenic disturbances. Pain of the oral mucosa can be also reflected (referred pain) from other parts of the body. Given the multitude of possible causes of intraoral pain as a component of orofacial pain, the diagnostic process is complex and requires a multidisciplinary approach. A prerequisite for establishing an accurate diagnosis is thorough knowledge of a wide spectrum of diagnostic characteristics of orofacial pain which include the origin and type of pain (somatic, neurogenic and psychogenic), duration (acute or chronic) and mechanisms of pain onset (nociceptive, neuropathic, psychosomatic) and their differentiation. The emphasis in this article is on differential diagnosis of the most common painful conditions of oral mucosa in respect to their clinical features.

**Key words:** orofacial pain; pain of oral mucosa; oral lesions; mucogingival pain; neuropathic pain; systemic diseases; differential diagnostics.

### DEFINING PAIN

Pain is a multidimensional subjective experience and more than just tissue damage contributes to the patient's expression and rating of pain response [1].

There are patients who rate their oral pain as being unbearable, yet have only very mild or clinically barely evident mucosal changes. On the other hand pati-

ents with severe, extensive mucosal lesions report minimal oral pain and can function normally. The fact that different people exposed to the same stimuli feel pain and react to it completely different, and that some people are less sensitive to pain than others, can be explained in the light of recent scientific discovery.

A publication of a paper in the journal *Nature Medicine* brought a major new insight into the molecular mechanisms of pain [2]. Scientists have identified a "pain gene" that explains why certain individuals are less sensitive to acute pain and less likely to develop chronic pain. The affected gene is called GCH1, which codes for an enzyme called GTP cyclohydrolase. This enzyme is needed to produce a chemical called tetrahydrobiopterin or BH4. They discovered that a pathway that produces BH4 is significantly activated during pain states. When the researchers inhibit BH4 production in experimental models, they relieve pain and when they administer BH4, they produce pain.

The authors also identified a link between reduced pain sensitivity and people carrying a mutation in the human gene responsible for BH4 production. At least one copy of this pain protective form of the gene is present in 20-25% of the human population. A subset of this group, representing approximately 3% of the human population, carry two copies of the gene and experience significantly less pain after disc surgery than those carrying a single copy.

Administering inhibitors of GTP cyclohydrolase (the critical enzyme in BH4 production) to reduce the elevated BH4 levels in pain conditions could mimic the effect of the pain protective form of the gene and lead to a disease-modifying pain therapy.

Therefore this data also suggest that individuals who say they feel less pain are not just stoics but genuinely have inherited a molecular machinery that reduces their perception of pain. This difference results not from personality or culture, but real differences in the biology of the sensory nervous system.

## ETIOLOGY OF OROFACIAL PAIN

Pain in the orofacial region is frequent complaint. It can be a symptom of a broad spectrum of various acute and chronic diseases and recurrent painful disorders, or it can represent a disease *per se*. As a symptom, it may occur due to the diseases of the oral tissues, temporomandibular joint, salivary glands, musculoskeletal, vascular and neurologic disorders of the head and neck, or psychological abnormality [3].

The pain may also be referred from other sources; cervical spine, intracranial pathology, systemic disease; or it may occur in the absence of detectable abnormalities, termed atypical, idiopathic or non-somatic pain [4].

Although in some cases there is no pathological evident cause for the pain, the sensation felt by the patient is very real [1]. Patients suffering from this kind of pain are frequently described as having underlying psychiatric disturbances [5,6].

Because of the diversity of causes and complexity of anatomic structures involved, patients with oral pain represents diagnostic and therapeutic challenge to dentists professionals.

Since the epidemiological studies revealed that 10%-50% of the adult population experienced orofacial pain on a daily basis, increasing frequency of different orofacial painful syndromes in the general population makes the role of the dentist increasingly important in the treatment of orofacial pain [7-10].

## DIAGNOSTICS OF ORAL MUCOSA PAIN

Diagnostic evaluation of patient with oral mucosal pain includes a careful and thorough dental and medical history, review of systems and physical examination of the integrity and function of oral mucosa and surrounding tissues with special attention to the temporomandibular joint (TMJ) and muscles and the cranial and cervical muscles and nerves. [3,12-17].

The most important part of the diagnostic procedure is history in which description of pain characteristics may serve as the basis for the diagnosis and treatment. They include informations about: origin of pain, duration, localization and intensity, type of tissue that is affected by pain or is damaged and cause pain as well as etiology of pain. For the purpose of proper treatment, it is important to determine duration of pain and distinguish acute pain from chronic.

Acute pain is almost always associated with a known cause of tissue damage. Oral mucosa is constantly exposed to local irritation and lesions occurs due to local injury, inflammation or infection and in some cases due to presence or egzacerbation of underlying systemic disease.

Acute pain has a distinctive flow, disappears after the removal of the cause and treatment of damaged areas. It has a primarily biological purpose and is therefore considered "good" pain since it serves as a protective mechanism or a warning sign. It begins suddenly, has a short duration and can be usually easily diagnosed. Acute pain responds to an usual medical and dental treatment methods. If not diagnosed and treated appropriately, acute pain can skip to the chronic [11,12].

If pain lasts longer than 3 months and outlasts the inflammatory stimulus, it is considered chronic pain [3,4,11]. Unlike acute pain, chronic pain has no bio-

logical purpose, it is not self-limited and runs continuously. Treatment methods that are effective for acute pain are often unsuccessful in treating chronic pain, and sometimes contraindicated. As pain lasts, gives rise to more responses of the central nervous system, and concomitant psychological factors intensify clinical characteristics. While acute pain accompanies the feeling of anxiety and discomfort, chronic pain is characterized by a feeling of dejection and depression. Acute pain is considered a symptom of illness, and chronic pain represents disease of itself [3,4,12].

During history it is necessary to collect relevant data about existence of systematic diseases, including the results of earlier examinations and treatment and list of drugs that patient takes. This is particularly important while many systemic diseases contribute to the development of painful oral conditions (Table 1). It is also well documented that some medications (lisinopril, isoniazid, vincristine, phenytoin, nitrofurantoin, cisplatinum, amiodarone; oral contraceptive, etc.) may cause peripheral neuropathy and paresthesia [14]. Furthermore, it is necessary to detect factors associated with present pain, that cause pain, worsen or reduce it or pain is its negative consequence [12]. Evaluation should include a review for a history of primary headaches, surgeries, traumas, and stressors [15,16].

A review of daily activities, habits as well as parafunctional oral habits, and sleep patterns should be included. Examination of the oral cavity should include inspection of all regions of oral mucosa to detect mucosal lesions and palpation to examine sensitivity of oral mucosa and trigger points as well as other diagnostic procedures to determine the presence of unpleasant and painful symptoms [3,17-19].

**Table 1.** Systemic diseases associated with orofacial pain

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Cardiac ischemia	Hyperthyroidism
GERD	Hyperparathyroidism
Diabetes mellitus	Systemic lupus erythematosus
Vitamin B deficiencies	Multiple myeloma
Folic acid and iron deficiency anemias	Cancer therapy
Paget's disease	Metastatic disease

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MRI and computed tomography (CT) scan of the TMJs may be necessary to evaluate possible advanced degenerative pathologies or tumors in orofacial region in the case of neuropathic pain, treatment-resistant chronic pain and unusual pain patterns [3,12,15]. Consideration of other diagnoses by history and physical exam and laboratory studies will dictate additional studies and referral to the appropriate specialist [3,15].

Obtaining a medical history from each patient with orofacial pain should be a routine procedure in dental office. It gives the dentist an insight into the past and present physical health of the patient, and this information is of great importance in terms of diagnosis and treatment of orofacial pain (Table 1).

## **PAIN CATEGORIES**

Using informations obtained from the diagnostic process orofacial pain can be classified by duration in *acute* and *chronic* pain and by its origin in three basic categories: *somatic*, *neuropathic*, and *psychogenic* pain [20-22].

### **Somatic pain**

Somatic pain results from noxious stimulation of normal neural structures that innervate the affected area and is divided into superficial or deep somatic pain.

*Superficial somatic pain* has a bright and stimulating quality, is primarily involved in acute pain conditions and usually does not present any diagnostic difficulty.

Numerous local and systemic factors can cause damage and consequently acute inflammatory reaction in the oral mucosa with release of inflammatory substances that act causing pain. The nature of painful symptoms depends on the type of stimuli, the extent and location of injury, the injured tissue reactivity and stage of inflammation. Pain due to inflammation occurs mainly due to the action of histamine and bradykinin, substances that are released during inflammation, stimulate nociceptors and reduce their threshold. This substances together increase local vazodilatation and capillary permeability, causing edema that mechanically stimulate receptors and causes pain. As the threshold of pain decreased, nociceptors become more sensitive to stimuli. As a result, stimulus-induced primary hyperalgesia and spontaneous pain occurs [23,24]. This type of pain is classified as *superficial somatic pain* or *mucogingival pain* and occurs in damaged oral mucosa.

In contrast, deep somatic pain arises from damaged deeper body structures, has a dull, deep, depressing quality, and frequently exhibits CNS secondary excitatory effects such as referred pain to other sites and local autonomic effects (e.g., odontogenic pain, musculoskeletal pain), [22].

### **Neuropathic Pain**

Neuropathic pain occurs due to a structural abnormality in one or more components of the nervous system that innervate the affected area. It can arise

spontaneously in the absence of any obvious noxious stimulation and is usually described as bright, stimulating, and burning. Neuropathic pain may be accompanied by paresthesia along a distinct nerve distribution. Severity of the pain is often out of proportion to the degree of stimulation; even light touch can cause intense pain [22].

Neuropathic pain may be paroxysmal and continuous disorders [20,22], (Table 2). The most common paroxysmal facial pain is trigeminal neuralgia (TN). Continuous neuropathic disorders are characterized by constant, unremitting pain of variable intensity. The pain usually has a burning quality and may be accompanied by paresthesia (abnormal sensation) or dysesthesia (unpleasant sensation). An example of a continuous neuropathic disorder is atypical odontalgia (AO), also known as phantom tooth pain. AO refers to persistent pain in apparently normal teeth and surrounding alveolar bone, or at extraction sites from which teeth have been removed because of pain [25], (Table 2).

**Table 2.** Neuropathic pain

<b>Paroxysmal</b>	<b>Continuous</b>
Trigeminal neuralgia	Postherpetic neuralgia
Glossopharyngeal neuralgia	Post-traumatic neuralgia
Nervus intermedius neuralgia	Atypical odontalgia
Occipital neuralgia	
Neuroma	

## **PSYCHOGENIC PAIN**

Psychogenic pain occurs due to psychological causes and it is not elicited by noxious stimuli or any abnormality within the nervous system. Although the patient report on pain, there is no apparent oral lesion responsible for the pain. Psychological factors are involved in the etiology, and a definite history of emotional or personality disorder is present [22]. Because an anatomic relationship between the pain source and the site of pain is absent, psychogenic pain may be felt in many areas, the location varying during the disease process. The degree of pain expressed by the patient is often exaggerated, and response to treatment is usually inconsistent [3,6,16].

## **MUCOGINGIVAL PAIN WITH RECOGNIZED ORAL LESION**

### **Mouth sores**

Over a third of acute orofacial pain syndromes are caused by mouth sores. Lesions of oral mucosa are caused by various factors, among most common are viral

and bacterial infections, local injuries and inflammation as well as underlying systemic disease. While the differential diagnostics is extensive, the following are among the most common causes of oral mucogingival pain: [3,28], (Table 3).

**Table 3.** Differential diagnostics of most common oral causes of mucogingival pain

PERIODONTAL DISEASES	RECURRING ORAL ULCERS
Acute necrotizing ulcerative gingivitis (ANUG);	Recurrent aphthous stomatitis
Periodontal abscessus	Behçet's syndrome
	Recurrent herpes simplex virus infection
ACUTE MULTIPLE LESIONS	CHRONIC MULTIPLE LESIONS
Herpesvirus infections	Pemphigus
Primary herpes simplex virus infections	Subepithelial bullous dermatoses
Coxsackievirus infections	Herpes simplex virus infection in immunosuppressed patients
Varicella-zoster virus infection	
Erythema multiforme	
Contact allergic stomatitis	
Oral ulcers secondary to cancer chemotherapy (Mucositis)	SINGLE ULCERS
	Anaerobic infections of oral mucosa
	Deep mycoses
	Systemic diseases (inflammatory bowel disease)

### Mucositis vs Stomatitis

The terms stomatitis and oral mucositis are often used as synonyms, but they do not reflect identical processes. Stomatitis refers to any inflammatory condition of oral mucosa which occurs due to local infections or injuries or underlying systemic diseases.

Oral tissue damage and mucositis pain can be a significant problem for patients undergoing anticancer therapy. Oral mucositis describes inflammation of oral mucosa resulting from chemotherapeutic agents or ionizing radiation. The frequency and severity of these problems can vary significantly with the type and dose of therapy.

It has been reported that mucositis developed in 22% of 1236 cycles of chemotherapy and in approximately 75–80% of patients who receive high-dose chemotherapy prior to hematopoietic cell transplantation. The pathogenesis of oral mucositis is multifactorial; a complex five-stage model is proposed in the development of mucositis. [29,30-32].

Lesions of oral mucositis are often very painful and typically manifests as erythema or ulcerations which appear 7 to 10 days after initiation of high-dose

anticancer therapy. Mucositis may be exacerbated by local factors and infections. Infections associated with the oral mucositis lesions can cause life-threatening systemic sepsis during periods of profound immunosuppression. When uncomplicated by infection mucositis heals within 2 to 4 weeks after cessation of cytotoxic chemotherapy.

While oral complications primarily are associated with discomfort and interference with oral function, and quality of life [33] in patients who are also immunocompromised or debilitated, these complications can become life threatening. Thus, management of mucositis pain is a primary component of any mucositis management strategy [30,31].

## **NEUROPATHIC PAIN WITHOUT VISIBLE MUCOSAL LESION**

Patients who have no evident clinical lesions or pathological changes on oral mucosa and suffer pain are the most difficult patients for treatment. In such cases, a pain originates from a structural abnormality in one or more components of the nervous system that innervate the affected area and is termed neuropathic pain.

The most common neuropathic pain syndromes in the orofacial region include trigeminal neuralgia; traumatic neuropathy; trigeminal neuroma; postherpetic neuralgia; diabetic neuropathy; cancer-related neuropathy, neuropathy induced by acquired immunodeficiency syndrome or AIDS; and chronic continuous trigeminal nociceptor neuropathy (with and without sympathetic mediation), [34].

### **Burning mouth syndrome**

*Burning mouth syndrome* (BMS) is one of the most common painful disorders of the oral mucosa and represents very unpleasant oral condition. It has the characteristics of the surface somatic pain, although recent studies suggest a neuropathic basis of this syndrome [35].

The International Association for the study of Pain defines BMS as chronic painful syndrom since pain lasts at least 4-6 months located on the tongue or other mucosal membranes in the absence of clinical or laboratory findings [1].

BMS is characterized by a sensation of stinging and burning although the subjective experience and description of the symptoms among different patients vary from pricking, tingling, itching, annealing to paresthesia sensations and numbness of oral mucosa. These symptoms occur almost always in the absence of clinically detectable or visible damage of oral mucosa, which complicates dia-



gnosis and causal treatment. Significant feature of this situation is that location of pain is at the site of less movement of oral mucosa and its maximum exposure to trauma. With time, on this sites hyperemia may occur as a sign of irritation and inflammation followed by epithelial desquamation and ulceration. Clinical picture may be further complicated by secondary infection of damaged tissue. This situation may worsen, but calm down probably because of inhibitory effect of pain on the further mobility of mucosa and its damage.

Since the most affected area is the tongue (tip and lateral borders), terms ‘glossodynia’ (painful tongue) and glossopyrosis (burning tongue) and glosalgia are commonly used; other terms such as stomatodynia, stomatopyrosis, oral dysesthesia are synonyms for burning mouth syndrome. BMS is frequently associated with other unpleasant oral symptoms xerostomia (dryness of the mouth) and dysgeusia (taste alterations). Burning mouth syndrome is characterized by being continuous and spontaneous with episodes of burning sensation of varying intensity [35,36].

Prevalence of BMS varies between 0.7 and 12,2% in general population [35-40]. The condition primarily affects women, ratio is approximately 3:1 in respect to men.

**Table 4.** Most frequent etiologic factors in *burning mouth syndrome* (Adopted from ref. 32)

<b>Local factors</b>	<b>Systemic factors</b>	<b>Psychological factors</b>	<b>Idiopathic factors</b>
Poorly fitting dentures	Endocrine alterations:	Anxiety;	
Parafunctional habits;	(hypothyroidism, diabetes	Depression;	
Dental anomalies;	mellitus, menopause);	Compulsive disorders;	
Contact allergic reactions;	Deficiencies (Fe, vit. B	Psychosocial stress;	
Infection;	complex, zinc);	Cancerphobia.	
Chemical factors;	Anemia;		
Galvanism;	Gastrointestinal anomalies;		
Taste alterations;	Esophageal reflux;		
Xerostomia.	Medication;		
	Neuropathy;		
	Sjögren’s syndrome.		

The etiology of BMS is complex and involves local, systemic and psychological factors (Table 4). Frequently several factors coincide, increasing the harmful effect on the mucosa. Approximately 17% to 33% of patients attribute the initiation of the symptoms to a previous condition, such as infection, dental procedure or the use of medications. Other patients relate the appearance of symptoms

directly with stress [38,40]. Local factors have a direct irritant effect on the oral mucosa, causing injury and pain which is considered to be mucogingival pain. Recent neurophysiological studies suggest that the central and/or peripheral nervous system are implicated in the pain of BMS [39,41]. Central neuropathic mechanisms have been demonstrated following thermal stimulation of the trigeminal nerve in patients with BMS. Patients with BMS show patterns of cerebral activity similar to those that appear in other neuropathic pain disorders, suggesting that the cerebral hypoactivity could be an important element in the pathogenesis of BMS, and indicating that pain in BMS is of neuropathic origin [35,36,42,43].

## NECK-TONGUE SYNDROME

Although rarely diagnosed, *neck-tongue syndrome* (NTS) deserves much attention since often, cervical spine involvement is misdiagnosed or unrecognized source of orofacial pain, particularly in the case when paresthesia in tongue is present. Neck tongue syndrome is characterized by unilateral paroxysmal neck pain in association with ipsilateral paresthesia (numbness) of the tongue [44,45]. It is triggered by rotation of the neck, usually to the same side as the sensory signs. The tongue manifestations arise from sensory fibers, including proprioceptive afferents originating in the lingual nerve, which joins the dorsal roots of C2 by way of hypoglossal nerve [44]. Neck and tongue symptoms will dissipate in approximately 60 seconds [45]. The classic presentation of symptoms is brought on by a brisk, sudden axial rotation of the head. It may be associated with pathologic findings in the region of the first two cervical vertebrae.

Malformations, degenerative processes, and tumours may result in compression of the C2 root [46]. Irritation of the C2 cervical root appears to be a likely cause of most of the manifestations. NTS has been reported over a wide age range [6-65 years). There is no clear sex or age predilection. Minority of cases have reported an onset prior to 20 years of age [47].

The communication of the hypoglossal nerve with the sympathetic trunk, the vagus, and the first and second cervical and lingual nerves explains the sensory signs in the oropharyngeal area. The trigeminal involvement is not likely because of the lack of evidence for anatomic closeness with either the hypoglossal nerve or the upper cervical roots. In the absence of pathologic findings requiring specific therapy, the disorder appears benign and conservative management is effective. Conservative treatment includes avoidance of neck trauma and the use of anti-inflammatory agents and drugs to alleviate neuropathic pain [45,47].

## **Trigeminal neuralgia**

*Trigeminal neuralgia* (TN), also called *tic douloureux*, is the most common of the cranial neuralgias and chiefly affects individuals older than 50 years of age. In younger individuals

suspicion of a detectable underlying lesion such as a tumor, an aneurysm, or multiple sclerosis must be increased [48].

Trigeminal neuralgia is characterized by sudden, stabbing, and severe unilateral facial pain and intraoral pain in innervation field of affected branch of one of three divisions of the trigeminal nerve. The most prominent feature of trigeminal neuralgia is the existence of trigger points often located in the skin of the lips, cheeks or gums and when touched may provoke a painful stimulus. Onset is frequently triggered by mechanical stimulation such as talking, chewing, or touch. Attacks can last from seconds to a few minutes. Periods of attacks can last weeks or months, followed by periods of remission for months or years. Incidence increases with age, and middle aged women are most commonly affected [49].

Except possible compression of the trigeminal root by a vessel or tumor or virus infection, little information is available about the etiology of trigeminal neuralgia.

Imaging diagnostics (CT, MR) is an important for excluding intracranial pathology and multiple sclerosis (MS) [15,50], particularly in younger patients with symptoms. Novel MRI studies can reveal demyelinating lesions of the white matter associated with MS [51]. Some of the surgical approaches to the treatment of trigeminal neuralgia include microvascular decompression, radiofrequency rhizotomy, and gamma knife surgery [53].

## **Acute and post-herpetic neuralgia**

*Acute herpetic neuralgia* (AHN) may affect one of three divisions of the trigeminal nerve and if occur in the mouth, maxillary and mandibular branches are involved. After the primary infection with Varicella zoster virus (VZV) and healing of mucosal and cutaneous lesions, virus becomes latent in the dorsal root ganglia of spinal nerves or extramedullary ganglia of cranial nerves. Virus reactivation in some period of life cause Herpes zoster (HZ) with occurrence of vesicles on affected oral mucosa and skin which are innervated by affected branch of trigeminal nerve. Pain that follows eruption of vesicles is always unilateral and may be recurrent with lancinating episodes; it is well-localized to the affected site and described as burning or itching, frequently associated with hyperesthesia and hyperalgesia. The most common complication of HZ is postherpetic

neuralgia (PHN), which is defined as pain remaining for over a month after the mucocutaneous lesions of Herpes zoster have healed.

The pain of PHN is diffuse, dull, and aching, with a superficial allodynic sensation evoked by touch and clothes. Diagnosis is clinical and based on the presence or past presence of vesicles. A more difficult diagnostic problem is severe pain caused by VZ virus without lesions developing along the course of the nerve (*zoster sine herpette*; *zoster sine eruptione*). Diagnosis in these cases is based on clinical symptoms and serologic evidence of a rising antibody titer [54], (Table 5).

**Table 5.** Trigeminal neuropathic pain disorders (Adopted from ref. 52 and modified)

Diagnosis	Trigeminal neuralgia	Deafferentation pain	Acute and post-herpetic neuralgia	Burning mouth syndrome
<b>Diagnostic features</b>	Brief severe lancinating pain evoked by mechanical stimulation of trigger zone (pain-free between attacks). Usually unilateral, affects the n.V2/V3 areas (rarely n.V1). Possible pain remission periods (for months/years).	Spontaneous or evoked pain with prolonged after-sensation after tactile stimulation. Trigger zone due to surgery (tooth extraction) or trauma. Positive and negative descriptors (eg, burning, nagging, boring).	Pain associated with herpetic lesions, usually in the n.V/1 dermatome. Spontaneous pain (burning and tingling), but may present as dull and aching. Occasional lancinating evoked pain.	Constant burning pain of the mucous membranes of the tongue, mouth, hard or soft palate, or lips. Usually affects women age >50 years.
<b>Diagnostic evaluation</b>	MRI for evidence of tumor or vasocompression of the trigeminal tract or root (cerebropontine angle). Rule-out MS, especially in young adults.	Etiologic factors such as trauma or surgery in the painful area. Order MRI if the area is intact to rule-out peripheral or central lesions.	Small cutaneous and mucosal vesicles (AHN) or scarring (PHN), usually affecting n.V/1. Loss of normal skin color. Oral ulceration can occur. Sensory changes in affected area (eg, hyperesthesia, dysesthesia).	Rule-out salivary gland dysfunction (xerostomia) or tumor, candidiasis, local irritation. Nutritional deficiencies and menopause

## REFERRED PAIN

Referred pain to the orofacial region is an important clinical consideration. The location of pain, therefore, will not always correspond to its source. A mechanism that has been proposed to explain referred pain is convergence in which

primary afferent fibers from different sites converge on the same second-order neuron in the brainstem nucleus [55].

## ASSOCIATION OF ORAL PAIN WITH SYSTEMIC DISEASES

Many studies have reported an association between orofacial pain, systemic diseases or disorders and general pain conditions [56-59]. Although the prevalence of comorbid systemic conditions, except some specific psychological disturbances and generalized musculoskeletal disorders, has been studied weakly in orofacial pain populations, there are some studies that indicate on this relationship. Medical conditions that have suggested links with orofacial pain include cardiovascular disease [60-63], headache, ear, nose and throat symptoms, neck pain, gastrointestinal disorders, musculoskeletal conditions such as fibromyalgia, chronic fatigue syndrome and rheumatoid arthritis, and psychological disturbances [16,58].

The study of de Leeuw et al. [64] provided evidence that female patients with orofacial pain appear to have more systemic problems than do female patients seeking routine dental care. A possible hypothesis for this finding may be that orofacial pain shares a pathophysiology with more systemic functional and generalized musculoskeletal disorders.

Clinical investigation of the majority of patients referred after initial evaluation of an unsolved oral complaint only rarely detects undiagnosed systemic disease. On the other hand, treating systemic disease, does not always eliminate the oral symptoms. Referral consultations for unexplained oral complaints may thus result in recommendations for additional treatment of systemic disease noted at the time of consultation such as in the case of psychiatric disturbances [5,15,19].

Although in some diseases, such as hyperparathyroidism, plasmacytoma, Paget disease and metastatic diseases, radiological and laboratory findings will reveal disease, in other cases, oral pain may be the first indication of the early stage of disease (e.g., jaw pain in angina pectoris), [63].

Pain in the craniofacial structures can be the only complaint during cardiac ischemia and acute myocardial infarction (AMI). In the study of Kreiner et al. [61] the most common craniofacial pain site was the throat, followed by the mandible, the TMJs and ears, neck, and teeth. Jaw pain induced by cardiac ischemia tend to occur bilaterally as opposed to the pain of odontogenic origin which rarely crosses the midline. Therefore, in differential diagnosis of orofacial and dental pain, craniofacial pain should be also considered.

Failure to recognize cardiac pain which is referred to face, head, neck, mouth and teeth can lead to treatment delay that can put the patient's life at risk.

The presence of systemic conditions in a patient with orofacial pain may influence and limit the treatment options and compromise treatment outcomes. Treatment of patients with orofacial pain and with complex systemic diseases should be directed toward both the orofacial pain complaint, as well as the concomitant medical conditions. Therefore, patients with more medically complicated orofacial pain, should be treated multidisciplinary.

## **DIFFERENTIAL DIAGNOSTICS OF OROFACIAL PAIN IN ELDERLY**

Some pathologic conditions are more prevalent in older people than in younger as a result of aging although aging alone does not necessarily mean disease. Oral health and function is commonly altered in older adults. Older people often have a variety of simultaneous health problems and take a variety of medications, and this makes it often difficult for the dentist to make a definitive diagnosis of oral pain. Differential diagnosis of oral pain in the elderly should include infections, neoplasms, cardiovascular, gastroenterologic, neurologic, traumatic, musculoskeletal or psychological diseases.

The presence of jaw pain related to cardiac causes underlines the importance of carefully recording patient's history, and relevant symptoms. Angina pectoris can be determined if chest pain occurs at rest or during activity. The pain of angina pectoris may arise in or radiate to the neck, jaws, throat, occipital region, cheek, ear pinna, mastoid process, external auditory canal, shoulders, upper and lower arms, hands or epigastrium. Typically, the pain radiates to the left side of the jaw and the left shoulder. Angina pain is located primarily in the lower jaw and even occasionally the upper jaw.

Cranial (giant cell or temporal) arteritis is a granulomatous vascular inflammatory disorder that affects medium or large cranial arteries. Perioral symptoms include pain of the masticatory muscles, facial edema that can mimic infection or muscular hypertrophy. In addition, claudication of the tongue can occur due to involvement of the lingual artery.

Paget's disease of the bone usually affects an elderly population. Disease is characterized with facial pain but also signs of atypical trigeminal neuralgia may be present in addition to possible facial nerve palsies and hearing deficits [66].

The prevalence of cancer rises with advancing age, and pain is a common complaint of those with cancer. The elderly, especially those older than 85, are at risk for undertreatment of pain. Oral cancer present with a variety of symp-

toms among which pain is not the first sign, rather it occurs late in the course of the disease. Local tumor growth and invasion result in local tissue destruction, secondary infection, nerve compression and myofascial pain. Pain occurs after surgery due to nerve damage, and inadequate vascularization of myocutaneous flaps; after radiation and chemotherapy due to neuritis, osteoradionecrosis, damaged salivary glands, secondary infection and mucositis. Physical condition may be complicated by psychogenic factors, fear and anxiety of tumour recurrence, which along with emotional distress regarding cosmetic concerns may contribute to the overall pain response. Therefore, the approach in the diagnosis and treatment of these patients is always multidisciplinary [67].

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## Sažetak

### Diferencijalna dijagnostika bolnih stanja sluznice usne šupljine

Orofacijalna bol česta je i dijagnostički zahtjevna tegoba. Među brojnim uzrocima orofacijalne boli najčešći su bolesti zuba i parodonta, a po tom i različite bolesti sluznice usne šupljine. Bol sluznice usne šupljine prateći je simptom različitih oštećenja sluznice uzrokovanih lokalnim ili sustavnim čimbenicima. Bol oštećene sluznice spada u kategoriju somatske površinske boli i naziva se mukogingivna bol. Međutim, bol sluznice može biti prisutna i u odsutnosti patološkog nalaza. Tada je riječ o neuropatskoj boli koja je posljedica oštećenja dijela živčanog sustava ili je bol psihogenog podrijetla. Bol sluznice usne šupljine može biti i odražena (refleksna bol) iz drugih dijelova tijela. S obzirom na mnoštvo mogućih uzroka orofacijalne boli, dijagnostički je postupak složen i zahtijeva multidisciplinarni pristup. Preduvjet za postavljanje točne dijagnoze jest poznavanje širokog spektra dijagnostičkih karakteristika orofacijalne boli, koje uključuje podrijetlo i vrstu boli (somatska, neurogena i psihogena), trajanje (akutna i kronična) i mehanizme nastanka boli (nociceptorska, neuropatska, psihosomatska) te njihovo razlikovanje. U ovome radu prikazana su različita bolna stanja sluznice usne šupljine i njihove diferencijalnodijagnostički bitne karakteristike.

**Ključne riječi:** orofacijalna bol; bol sluznice usne šupljine; lezije sluznice usne šupljine; mukogingivna bol; neuropatska bol; sustavne bolesti; diferencijalna dijagnostika.

