Differential diagnosis of toothache to prevent erroneous and unnecessary dental treatment.

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Abstract :

Toothache represents the most common example of orofacial pain. Its origin is mostly odontogenic, but several other conditions may mimic dental pain or present themselves as such. Well-known examples are myofascial pain, trigeminal neuropathies like neuralgia and painful posttraumatic trigeminal neuropathic pain, orofacial neurovascular pains, cardiac pain and sinus disease. This review first discusses the current knowledge on the underlying pathophysiology of heterotopic tooth pain. Afterwards, several conditions potentially presenting as toothache will be illustrated regarding clinical features, diagnosis and management.

Key words : dental pain – non-odontogenic toothache - referred pain

Introduction

Toothache and craniofacial pain are conditions affecting an important part of the population. A review on the prevalence of tooth pain and other oral pains [1] stated poor methodological quality of the epidemiologic studies, but concluded that 7-32 % of the population suffers from toothache and 40-44 % from oral and facial pain. In the United Kingdom, MacFarlane et al. [2] found 26 % of participants in a cross-sectional study reporting orofacial pain, from which 54 % continued to have pain at a follow-up 4 years later. Also in other countries chronic orofacial pain appears to be very frequent [3,4]. Evidently, in most patients toothache has its origin in caries, pulpal or periodontal involvement and these acute situations are managed by adequate dental care. However, in many instances, the symptom of toothache results from a non-odontogenic cause. As a result of misdiagnosis, a number of erroneous dental interventions may be performed by well-intentioned and caring practitioners[5], [6] and this should absolutely be avoided. In addition, the complicated differential diagnosis in these patients can be time-consuming and this adds to other risk factors (e.g. anxiety, catastrophizing [7] that allow pain to become chronic. After elaborating on the sometimes complicated diagnosis of odontogenic pain, this paper discusses current knowledge on the neurophysiological mechanisms underlying heterotopic pain. Afterwards, the clinical features of the most common causes for non-odontogenic toothache will be reviewed. More detailed and extensive descriptions of these conditions can be found in excellent text-books and papers that recently have been published[8, 9, 10,11].

Toothache and its complicated diagnosis

Dental pain is the most frequent cause of orofacial pain and still the most important reason why patients seek help with the dentist. The diagnosis of dental pain (caries, pulpitis, apical periodontitis) does not pose any problem in most patients: a comprehensive and thorough anamnesis comprising the history, the natural course, the provoking factors and the character of the pain will guide the trained dentist to a preliminary diagnosis, that in most cases easily is confirmed using the array of

available tools for clinical and radiological examination. The most relevant clinical diagnostic techniques are provocation tests and test-anesthesia. A fast, efficient and predictable solution can be offered in the majority of patients. However, numerous situations may complicate a clear diagnosis : the diverse irradiation patterns of pulpitis, the referred pain between different branches of the trigeminal nerve, the insidious characteristics of a cracked tooth or a root fracture, the potential impact of large (composite) restorations on the tooth pulp, the complex anatomy of multi-rooted teeth (recent developments like Cone Beam CT imaging allow to discriminate 5,6, even 7 root canals in a single tooth).Missing a diagnosis of dental pain may result in patients desperately seeking a solution for their ongoing pain, visiting specialists of various disciplines, using impressive doses of pain-killers, adding up (radiological) examinations. To limit the risk of such development, some important advices could be suggested in the diagnosis of dental pain :

- in every new patient presenting with orofacial pain, a thorough, complete and extensive history should be taken. . This anamnesis is crucial : the development of pain, its characteristics, the time course, the triggering, provoking and soothing factors, will provide the most important elements for a (preliminary) differential diagnosis. In addition an in-depth dental and periodontal clinical examination, supplemented with at least an overview picture of the dentition will provide sufficient information to exclude or pinpoint a dental pain.
- provocation tests (like air-drying a suspected tooth for 20-30 seconds, applying thermal, electrical or mechanical stimuli) may help significantly in triggering the familiar pain . However, the validity of some tools for sensibility testing of the pulp is questioned [12] .

The newly developed International Classification of Orofacial Pain (ICOP)[13] meticulously discriminates different kinds of pulpal pain and subclasses of reversible or irreversible pulpitis. Clear diagnostic criteria for each of them are provided and in addition, comments are offered detailing the diagnostic process and also the controversies regarding the correlation between symptoms and the differential diagnosis between reversible and irreversible pulpitis , and regarding the validity of some commonly used tools for sensibility testing.[14]

- in case a dental or periodontal cause is presumed, local anesthesia may be used to assist in determining the origin. If anesthesia does not result in pain reduction, the origin should be looked for elsewhere and treatment of the tooth should not be started. Still too often, erroneous endodontic (re-)treatment or extraction are performed.

Neurophysiology of heterotopic pain

Pain is defined "heterotopic" when the site where it is felt and reported by the patient, is not coincident with its source[15]. Traditionally, three kinds of heterotopic pain are described : central pain, projected pain and referred pain.

In case of *central pain*, a lesion or event within the brain or brainstem (e. g. a cerebrovascular accident) may damage nerve tissue that somatotopically corresponds to a particular region of the body. As a consequence, pain may be experienced in e.g. the orofacial region, while the source of pain is located in the central nervous system.

When a nerve is irritated or triggered at some point of its anatomical trajectory, the pain sensation follows the course of that nerve branch and is called a *projected pain*. The pain experienced in trigeminal neuralgia in case of a neurovascular conflict at the dorsal root entry zone, could be considered as such. It typically follows the 2nd and/or 3rd branch of the trigeminal nerve up to the midline of the face.

The third kind of heterotopic pain, *referred pain*, is considered of major importance in many of the deep pain states found in craniofacial pain (temporomandibular disorders, toothaches, headaches)[16]. Superficial nociceptive input converges with other afferent input from deep tissues and from cervical spinal afferents onto the second order neurons in the trigeminal brainstem sensory nuclear complex. Concomitant release of neurochemicals results in neuroplastic changes and an increased excitability of these neurons, termed central sensitization. In addition to underlying the

referred pain phenomenon, this process, if perpetuated, is considered a key factor in the genesis and continuation of chronic pain [15].

Non-odontogenic toothache

Among the more frequent kinds of non-odontogenic toothache are reported myofascial pain[17] , neuropathic pains of the trigeminal system [18] and neurovascular pains[19] . In addition, pain may originate from sinus problems [20], cardiac pathology[21] , neoplasia[22] and – rarely - secondary to a psychological disorder like schizophrenia[23]. For each of these potential causes, this section will summarize diagnostic and pathophysiological characteristics, as well the suggested management approach.

1. Myofascial pain with referral to the teeth.

The recent Diagnostic Criteria of Temporomandibular disorders (DC/TMD)[24] and the International Classification of Orofacial Pain (ICOP) [13] include the diagnoses of ' Chronic Primary Myofascial Pain with referral', where the classical report of pain in the jaw muscle in the history and during the clinical exam, is accompanied by a report of pain "at a site beyond the boundary of the muscle being palpated". Previous reports stated that provocation of this pain, familiar to the patient, was most easily initiated by palpation of "trigger points " or "taut bands" in the concerned muscle , while anesthesia of these trigger zones also eliminated the pain in the referred region[25]. Many of the concepts underlying the pathophysiology of trigger points and taut bands still lack validation : e.g. pain referral has been provoked in healthy volunteers after intense local pressure[26, 27], and locally no histological correlate of the trigger points, no biochemical changes, nor documentation via imaging were found. This is also the reason why these terms are not included in the DC/TMD or the ICOP. More recently, however, morphological and mechanical properties of the muscles were better described, changed electrical properties recorded and local biochemical changes reported[28]. A

better understanding of the biochemistry underlying peripheral and central sensitization of the nervous system, and the complex interaction between the anatomical and physiological state of muscles with nociceptive input upon the tissues[29], has clarified the clinical observations and effects regarding chronic primary myofascial pain (for review see [30]). As in most chronic pain syndromes, also disturbances of the autonomic nervous system [31], psychological factors (like anxiety or depression) and behavioral, environmental and genetic components contribute to its etiology and pathophysiology. In this regard, chronic primary myofascial pain fits in the model that was originally suggested by Diatchenko et al. [32] and convincingly supported by the results of the OPPERA studies[33]. Toothache in the maxillary or mandibular teeth is often reported by patients having chronic primary myofascial pain of the masticatory system[34]. The diagnosis of this referred pain is made by palpation of the jaw closing muscles, reproducing the familiar tooth-pain in the patient. Local anesthesia of the muscle traditionally is used both in the diagnosis and treatment of myofascial pain, although hard evidence is still lacking. In addition, management includes behavior modification, local therapy (massage, warmth), physical therapy, needling, splint therapy[35, 36,37, 38 ,39].

2. Trigeminal neuropathic pain.

The ICOP combines previous classifications of the IASP/ICD11 and the IHS/ ICHD [13] . Neuropathic pain is defined as " pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [40]. A distinction is made in Trigeminal neuralgia and Trigeminal neuropathic pain.

Trigeminal neuralgia may be of the "classical" type (in a pure paroxysmal form or concomitant with continuous facial pain), secondary to e.g. multiple sclerosis, a space-occupying lesion, some underlying disease, or idiopathic.

Trigeminal neuropathic pain can result from a viral infection (trigeminal post-herpetic neuralgia), trauma (post-traumatic trigeminal neuropathic pain, PTTNP) or from unknown origin (idiopathic trigeminal neuropathic pain). In PTTNP, neuroanatomically confined somatosensory abnormalities are mandatory, and these may be signs of hyper- or hypoesthesia [13]. This characteristic is not

required for other entities that have been described more recently : Persistent Dento-Alveolar Pain (PDAP) and persistent idiopathic facial pain (PIFP). The latter is the motivation to not classify PDAP and PIFP as orofacial neuropathic pains (ICOP [13]).

. Non-odontogenic toothache might occur in especially 3 of the above subgroups : classical trigeminal neuralgia (CTN), post-traumatic trigeminal neuropathic pain (PTTNP) and PDAP/PIFP.

a. Classical trigeminal neuralgia (CTN) [41]

Patients with CTN typically exhibit unilateral attacks of short, sharp, excruciating, shock-like pain of very high intensity over the trajectory of the 2nd and/or 3rd branch of the trigeminal nerve. The attacks may occur spontaneously, but mostly are triggered by innocent stimuli like touching a trigger zone, talking, chewing, cold or wind. In up to half of the patients, the paroxysms are superimposed on a more constant, dull, throbbing or burning pain of lower intensity. Regarding pathophysiology, amongst other theories, compression of the trigeminal nerve by an arterial or sometimes venous structure ("neurovascular compression, NVC") at the dorsal root entry zone is considered a major etiological factor, and this has been confirmed in many imaging and surgical studies [42] .

Since also chewing, tooth brushing and even gustatory stimuli (sweet or salt food [43]) may act as trigger, differential diagnosis with dental pain can be difficult. This warrants a thorough dental examination of each patient with a tentative diagnosis of CTN, and at the same time caution to engage in dental treatment without very convincing indication[44]. Indeed, patients often tend to blame a tooth in the concerned region and urge the dentist for extraction in view of pain intensity. Unfortunately, shortly after the extraction, the pain attacks start again[45]. CTN initially is managed using carbamazepine or oxcarbazepine. If these sodium-channel blockers are insufficient, add-ons like lamotrigine, baclofen, gabapentin or valproate and phenytoin have been suggested [46]. In case pharmacological treatment is unsuccessful or has too many side-effects, several surgical techniques are available (microvascular decompression, radiosurgical techniques, percutaneous destructive neurosurgical techniques)[47].

b. Post-traumatic trigeminal neuropathic Pain (PTTNP).

Non-odontogenic toothache may present at the onset or as part of a painful neuropathy developing after trauma or injury of a peripheral branch of the trigeminal nerve. Traumatic insults may be macrotrauma as in zygomatic fractures, but also implant surgery, removal of mandibular third molars, and even local anesthetic blocks or root canal therapy. Depending on the initiating procedure, incidences of 1 to 5 % were reported [48]. Even after comparable injuries, the onset of the pain and its characteristics may vary considerably, probably due to genetic, environmental and psychosocial factors [49]. The pain is mostly unilateral, confined to the dermatome of the nerve involved in the traumatic event, of moderate to severe intensity and mostly continuous with a burning or shooting character. Usually, the pain is accompanied with sensory disturbances (hypo- or hyperesthesia) that can be examined. In research settings, quantitative sensory testing (QST) may further elucidate the pathophysiology and validate further subgrouping based on the underlying mechanism, but this technique is difficult and laborious to employ in a classical clinical setting. In daily practice, however, it is still possible to gain important information regarding the nervous system (e.g. bilateral comparison regarding mechanical, thermal, pain thresholds) using readily available instruments. The development of PTTNP is thought to involve a series of events where inflammation, peripheral sensitization, ectopic firing of injured neurons, active involvement of glial cells and progressively increasing central sensitization (“wind up”) play an important role (for review see [50]).

Management of PTTNP is difficult, and even if pharmaca will improve quality of life and sleep, reduction of the pain was reported in only 11 % of patients [51]. In case topical application of lidocaine or capsaicin does not provide effective relief, classical systemic medication (antidepressants, anticonvulsants) is used [52].

c. Persistent idiopathic facial pain (PIFP) – Persistent dento-alveolar pain (PDAP)

For some decades, Atypical Facial Pain and Atypical Odontalgia were included in the pain classifications, representing a very heterogeneous group of patients not fulfilling the diagnostic

criteria for a more established diagnosis. Atypical Odontalgia was used for intraoral pain manifestations, while Atypical Facial Pain included the extraoral pains. More recently, in the ICOP, and as a result of better discrimination with other orofacial pains, the old definition of Atypical Facial Pain is abandoned and replaced by Persistent Idiopathic Facial Pain (PIFP), while also for its intraoral counterpart, the term Persistent Idiopatic Dento-alveolar Pain (PIDAP) describes more clearly the nature of this diagnosis. Both groups are very diverse in their characteristics : unilateral or bilateral, quasi continuously present, sometimes exacerbating in attacks or not, mostly not confined to a particular nerve trajectory (in contrast to CTN or PTTNP) [53,50]. Some controversy remains regarding the pathophysiology of PIFP and PDAP : while there is no indication of a NVC or major traumatic event in the history, the amount of sensory deficits recorded using QST and the abnormalities in brain-stem mediated reflexes or excitability were not consistent in all studies [54,55]. Since, in contrast to PTTNP, no neuroanatomically confined somatosensory abnormalities are mandatory, they are not considered neuropathic pains. The overall management and care of these patients is problematic and unsatisfactory [56]. Little evidence regarding treatment of PIFP is available, but usually antidepressant medication (tricyclic or selective serotonin/noradrenaline reuptake inhibitors) in combination with behavioral therapy reinforcing coping strategies, is advocated [57]. Some studies also report partial success using invasive approaches (gamma-knife surgery or thermocoagulation of the Gasserian Ganglion)[58].

3. Orofacial pain resembling presentations of primary headaches.

Primary headaches include the multiple types of migraine and the trigeminal autonomic cephalalgias (TACs). The diagnostic criteria for migraine in its diverse variants have been extensively described in the International Classification of Headache Disorders[59]. In general, the symptoms associated with these types of migraine [13] like nausea, photo- or phonophobia, fatigue, lacrimation, rhinorrhea, conjunctival injection, facilitate the diagnosis. Differences in duration and frequency of the attacks

and the accompanying signs and symptoms, allow to differentiate between subtypes, but most of them share the anatomical location of the frontal, periorbital, temporal, parietal or occipital regions. Irradiation of the pain to the maxillary teeth is not uncommon [19] . If the orofacial area is the focus of the pain, the newly developed ICOP refers to "Orofacial Migraine" and "Trigeminal autonomic orofacial pain".

Benoliel et al.[60] reported that half of a group of patients with orofacial migraine did not satisfy the criteria of the ICHD classification, since the irradiation pattern was the lower 2/3 of the face. This prompted these authors to introduce the term Neurovascular Orofacial Pain (NVOP), previously also described as "lower facial migraine". In the new International Classification of Orofacial Pain [13], NVOP is one of the subtypes of Orofacial Migraine, and further subdivided in a shortlasting and a longlasting type, depending on an attack duration of less or more than 4 hours [13] . The distinct nature of this group is described with following characteristics : mostly unilateral episodic attacks of intraoral pain, lasting from minutes to hours, mimicking toothache, with a throbbing character that may awake the patient from sleep, but without any dental pathology. In contrast to migraine, patients are older at the time of onset and even more predominantly female with a 3 : 1 ratio. Frequently there is cold allodynia of several teeth, and there is at least one autonomic sign like lacrimation, cheek swelling, rhinorrhea etc. Evidently, differential diagnosis with dental pain or pulpitis is difficult and necessitates careful dental examination. While NVOP may respond to NSAIDs, management is more efficient using amitriptyline, propranolol or the treatment algorithm for migraine [61].

Also the group of Trigeminal Autonomic Orofacial Pains (TAOP) may present clinically as toothache or may be interpreted as such. Especially Orofacial Cluster Attacks, Chronic Paroxysmal Hemifacial Pain and SUNFA (short lasting unilateral facial pain attacks with autonomic signs) should be considered in the differential diagnosis.

Orofacial cluster attacks, previously called Cluster headache is rare, occurs 4 times more in males than females, and usually presents unilaterally in the periorbital or fronto-temporal region. In the vast majority of patients, the attacks occur in clusters episodically : at least 2 clusters of 7 days to a year, separated by a pain-free period of at least a month. 15 % of these Cluster-patients suffer from the chronic form, in which the attacks last more than a year without or with shorter pain-free intervals [62]. The attacks of excruciating sharp, throbbing or pressure-like pain occur unilaterally, two to 8 times per day, last mostly 30-60 minutes and are accompanied by autonomic signs. In more than half of the patients nocturnal attacks occur about 90 minutes after falling asleep. The pain concentrates especially in the periorbital region and in the eye, but radiation to teeth, jaws and the ear is very common[63]. Alcohol can act as a trigger for an attack, as well as nitroglycerin administration, in these patients who in general are heavy smokers. Attacks may be aborted by inhaling pure oxygen or the use of abortive medication for migraine (triptans). Prophylactic medication includes verapamil, valproic acid and topiramate and sometimes prednisolone is added during the first weeks necessary to allow the prophylactic medication to take effect [64].

The clinical features of *Chronic Paroxysmal hemifacial pain* [65] are quite similar to Orofacial Cluster attacks, but the attacks are shorter (seconds to 30 minutes) and more frequent. Also here the pain occurs unilaterally, but autonomic phenomena may be bilateral and the frequency is equal in men and women. While also in paroxysmal hemifacial pain the main location of the pain is periorbital and periauricular, irradiation to the teeth, the neck, shoulder and arm has been reported. In contrast to orofacial cluster attacks, oxygen does not abort attacks while typically indomethacine (150-225 mg/day) is very effective after 1-2 days, and even can be considered a confirmation of the diagnosis.

A third variant of the TAOP to be considered in the differential diagnosis of toothache, are the *Short-lasting unilateral neuralgiform facial pain attacks (SUNPA)*. These attacks constitute the shortest attacks of the TAOPs, and are being described as a series of short stabs [66]. There should be at least 20 attacks (lasting from few to 600 seconds) in at least 1 period per day. The attacks are accompanied

by autonomic signs : if there is also conjunctival injection and lacrimation, one uses the definition "Short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing" (SUNCT). ~~if only one or none of these two autonomic signs are present, it is called "Short-lasting unilateral neuralgiform attacks" (SUNA).~~ The localization of SUNPA pain is similar to the other TAOPs, i.e. especially periorbital, with potential referral to the maxillary teeth. The classical treatment approach is lamotrigine, while also some effect has been reported using anticonvulsants (carbamazepine, topiramate, gabapentin).

Most importantly, in the framework of this paper's topic, the dentist or orofacial pain specialist must be sufficiently aware of the existence and importance of the neurovascular types of pain, in order to prevent unnecessary invasive dental treatment and unnecessary delays. The occurrence of autonomic signs and symptoms associated with the reported "toothache" should inspire to more detailed anamnesis and in case of suspicion of neurovascular pain or headache, this should be explored more in depth. The differential diagnosis between the different forms of migraine or TACs as well as the pharmacological approach may probably better be managed by a neurologist.

4. Sinus disease.

Periapical infection of the maxillary teeth may lead to painful odontogenic sinusitis or – in chronic form – to mucosal hyperplasia of the maxillary sinuses, that is only seldom painful. However, also the reverse is possible : irritation by a sinusitis or mucosal disease of the maxillary sinuses can irritate branches of the maxillary division of the trigeminal nerve that, in addition to the maxillary teeth, also serves the maxillary sinuses and the anterior two-third of the nose [8, 20] . Symptoms of this referred pain from the sinus include continuous pressure or pain of several upper teeth on one side, that increases while chewing, clenching, bending over, application of cold, walking the stairs or increasing pressure in the sinuses by coughing or sneezing [67]. Often, the toothache is accompanied by a (frontal) headache and ENT-symptoms like nasal congestion, evacuation of fluid or pus from the nose. The diagnosis of this sinogenic tooth pain is made on basis of the history and influencing factors, the

absence of clear dental pathology, the accompanying ENT signs and symptoms, imaging of the area and a consultation with an ENT-specialist for further examination (e.g. endoscopy) and management (clearing of the sinuses, culture of nasal fluid or pus, NSAIDs or antibiotics according to the diagnosis). Frequently, a multidisciplinary approach allows for more precise and faster diagnosis and management for this type of referred toothache. And again, the major role of the dentist or orofacial pain specialist is to be aware of the differential diagnosis and, because they are not typically trained to evaluate sino-nasal structures, to organize a prompt referral to the ENT-specialist [20].

5. Cardiac problems.

Myocardial infarction or cardiac ischemia may refer pain to the orofacial region, the throat and the teeth. While orofacial pain was never reported as the sole symptom of myocardial infarction in a study involving an emergency care unit [68], two studies in different populations [20,69] concluded that throat pain and orofacial pain occurred in 4 out of 10 patients with cardiac ischemia. In these studies, the orofacial/throat location was more commonly reported than the "classic" pain in the left arm, in those patients where no chest pain was present. Mostly, the orofacial pain is associated with pain in other locations (chest, back, arm, throat). Whether occasionally it might be present as sole symptom of cardiac pathology is still debated [70]. The pain is mostly described as pressing or burning, in contrast to dental pain that is throbbing and aching [71]. Bilateral pain was found 6 times more often than unilateral pain. Physical exercise evidently may be a provoking factor for the pain. If the combination of the anamnestic information concurs with the clinical absence of any dental origin, immediate referral to a cardiologist for examination, ECG and further management is very important.

6. Toothache attributed or secondary to a psychological disorder

While the interaction between chronic pain and psychological factors has been widely accepted and documented in the framework of the biopsychosocial model, there is no evidence that psychological or emotional factors can induce tooth pain. Rarely, somatoform disorder or schizophrenia may be expressed as pain in teeth [23]. In those patients, pain is present in multiple teeth with a sharp,

stabbing and intense character. The teeth appear sensitive to temperature without any identifiable dental pathology. this kind of toothache may be more probable in case of association with hallucinations or delusions [72]. For the dentist or orofacial pain specialist, it is important not to engage in (extra) dental treatment but to refer to the neuropsychiatrist.

7. Neoplasia.

Toothache as a result of neoplasia is rare but existent. While several primary tumors (Schwannoma, lymphoma or pontine tumors interfering with the course of the trigeminal nerve [22]) may be accompanied by tooth pain, especially metastatic cancer has been described as originating factor (breast carcinoma [73], metastatic renal cancer [74]). In addition, also chemotherapy may cause toothache[75]. In cases with a potential neoplastic etiology for dental pain, the anamnestic and clinical information usually does not point in a specific direction and often also neural functions in the region are compromised. A multidisciplinary approach supported by specific imaging techniques (CT, MRI), may result in early adequate diagnosis and management.

Conclusion

The wide range of etiological factors for odontogenic and non-odontogenic pain may complicate the differential diagnosis. A dental pain should always be excluded first, using systematic history taking and thorough dental, periodontal and intraoral examination. At least one overview picture of the orofacial region should allow to exclude local pathology. The anamnesis is crucial : listening to the patient, inquiring in a systematic way on the onset, course, intensity, character of the pain, the provoking and soothing factors, the associated symptoms. All possibilities should be kept open, and if needed the examination techniques should be expanded. However, doctor's delay should be prevented and consequently there should never be any doubt to work together with other medical disciplines.

References

[1] Pau AK, Croucher R, Marcenes W. Prevalence estimates and associated factors for dental pain: a review. Oral Health Prev Dent. 2003;1(3):209-20.

[2] MacFarlane TV, Blinkhorn AS, Davies RM, Ryan P, Worthington HV, MacFarlane GJ. Orofacial Pain : just another chronic pain ? Results from a population-based survey. Pain 2002;99:453-458.

[3] John MT, LeResche L, Koepsell TD, Hujoel P, Miglioretti DL, Michelelis W. Oral health-related quality of life in Germany. Eur J Oral Sci 2003;111:483-491.

[4] Dworkin SF, Huggins KH, LeResche L, Von Korff M, Howard J, Truelove E, Sommers E. Epidemiology of signs and symptoms in temporomandibular disorders : clinical signs in cases and controls. J Am Dent Assoc 1990;120:273-281.

[5] Ram S, Teruel A, Kumar SK, Clark G. Clinical characteristics and diagnosis of atypical odontalgia : implications for dentists. J am Dent assoc 2009; 140 : 223-8.

[6] Von Eckardstein KL, Keil M, rohde V. Unnecessary dental procedures as a consequence of trigeminal neuralgia. Neurosurg Rev 2015; 38 : 355-60.

[7] Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Diatchenko L, Dubner R, Bair E, Baraian C, Mack N, Slade GD, Maixner W. Psychological factors associated with development of TMD: the OPPERA prospective cohort study. J Pain. 2013 Dec;14(12 Suppl):T75-90. doi: 10.1016/j.jpain.2013.06.009.

[8] de Leeuw R, Klasser GD. Orofacial Pain. Guidelines for assessment, diagnosis and management. 6th Ed. Quintessence Publ. Chicago. 2018, Pp 14-15.

[9] Yatani H, Komiyama O, Matsuka Y, Wajima K, Muraoka W, Ikawa M, Sakamoto E, De Laat A, Heir GM. Systematic review and recommendation for nonodontogenic toothache. J Oral Rehabil 2014; 41:843-852.

[10] Sessle BJ. Orofacial Pain : recent advances in assessment, management and understanding of mechanisms. Washington DC : IASP Press, 2014.

[11] Sharav Y and Benoliel R. Orofacial pain and headache 2nd Ed. Chicago Quintessence Publ Co, 2015.

[12] Mejàre IA[1], Axelsson S, Davidson T, Frisk F, Hakeberg M, Kvist T, Norlund A, Petersson A, Portenier I, Sandberg H, Tranaeus S, Bergenholtz G. Diagnosis of the condition of the dental pulp: a systematic review. Int Endod J. 2012 Jul;45(7):597-613.

[13] HYPERLINK "https://www.ihs-headache.org/binary_data/3468_the-international-orofacial-pain-classification-committee-icop-1-beta-for-review.pdf" https://www.ihs-headache.org/binary_data/346

[14] List T, Mojir K, Svensson P, Pigg M. A new protocol to evaluate the effect of topical anesthesia. Anesth Prog. 2014;61(4):135-44.

[15] Sessle BJ. Acute and chronic craniofacial pain : brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. Crit rev Oral Biol Med. 2000;11:57-91.

[16] Chichorro JG, Porreca F, Sessle BJ. Mechanisms of craniofacial pain. Cephalalgia 2017; 37:613-626.

[17] Wright EF. Nonodontogenic toothaches. J Am Dent Assoc 2015;146 : 406-8.

[18] Law LS, Lilly JP. Trigeminal neuralgia mimicking odontogenic pain. A report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 80 : 96-100.

[19] Sharav Y, Katsavara Z, Charels A. Facial presentations of primary headache disorders. Cephalalgia 2017;17 :714-719.

[20] Shueb SS, Boyer HC, Nixdorf DR. Nonodontogenic “tooth pain” of nose and sinus origin. J am Dent Assoc 2016; 147: 457-459.

[21] Danesh-Sani SH, Danesh-Sani SA, Zia R, Faghihi S. Incidence of craniofacial pain of cardiac origin : results from a prospective multicentre study. Aust Dent J 2012;57:355-358.

[22] Khan H, Heir GM, Quek SY. Cerebellopontine angle (CPA) tumor mimicking dental pain following facial trauma. Cranio 2010; 28 : 205-208.

[23] Miura A, Tu TTH, Shinohara Y, Mikuzuki L, Kawasaki K, Sugawara S, Suga T, Watanabe T, Watanabe M, Umezaki Y, Yoshikawa T, Motomura H, Takenoshita M, Maeda H, Toyofuku A. Psychiatric comorbidities in patients with Atypical Odontalgia. J Psycosom Res 2018; 104: 35-40.

[24] Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet J-P, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks S, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythorntwaite J, Hollender L, Jensen R, John MT, De Laat A, deLeeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher C, Zakrzewska J, Dworkin SF. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: Recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. Journal of Oral & Facial Pain and Headache 2014;28:6-27

[25] Simons DG. New views of myofascial trigger points : etiology and diagnosis. Arch Phys Med Rehabil. 2008; 89 : 157-159.

[26] Exposto FG, Udagawa G, Naganawa T, Svensson P. Comparison of masseter muscle referred sensation after mechanical and glutamate stimulation : a randomized double-blind, controlled, cross-over study. Pain 2018; 159 :2649-2657.

[27] Masuda M, Iida T, Exposto FG, Baad-Hansen L, Kawara M, Komiyama O, Svensson P Referred Pain and Sensations Evoked by Standardized Palpation of the Masseter Muscle in Healthy Participants.J Oral Facial Pain Headache. 2018; 32 : 159-166.

[28] Shah JP, Danoff JV, Desai MJ, Parikh S, Nakamura LY, Phillips TM, Gerber LH. Biochemicals associated with pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. Arch Phys Med Rehabil 2008;89:16-23.

[29] Fernández-de-Las-Peñas C, Galán-Del-Río F, Alonso-Blanco C, Jiménez-García R, Arendt-Nielsen L, Svensson P. Referred pain from muscle trigger points in the masticatory and neck-shoulder musculature in women with temporomandibular disorders. J Pain. 2010;11:1295-304.

[30] Fricton J. Myofascial pain.Mechanisms to management. Oral Maxillofacial Surg Clin N Am 2016;28:289-311.

[31] Passatore M, Roatta S. Influence of sympathetic nervous system on sensorimotor function : whiplash associated disorders (WAD) as a model. Eur J Appl Physiol 2006;98 : 423-449.

[32] Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders--pathways of vulnerability. Pain. 2006;123:226-30.

[33] Slade GD, Ohrbach R, Greenspan JD, Fillingim RB, Bair E, Sanders AE, Dubner R, Diatchenko L, Meloto CB, Smith S, Maixner W. Painful Temporomandibular Disorder: Decade of Discovery from OPPERA Studies. J Dent Res. 2016;95:1084-92.

[34] Wright EF. Referred craniofacial pain patterns in patients with temporomandibular disorder. J Am Dent Assoc. 2000 Sep;131(9):1307-15

[35] De Laat A, Stappaerts K, Papy S. Counseling and physical therapy as treatment for myofascial pain of the masticatory system. J Orofac Pain. 2003;17:42-9.

[36] Michelotti A, Steenks MH, Farella M, Parisini F, Cimino R, Martina R. The additional value of a home physical therapy regimen versus patient education only for the treatment of myofascial pain of the jaw muscles: short-term results of a randomized clinical trial. J Orofac Pain. 2004;18:114-25.

[37] Simons DG. Review of enigmatic MTrPs as a common cause of enigmatic musculoskeletal pain and dysfunction. J Electromyogr Kinesiol. 2004;14:95-107.

[38] Graboski CL, Gray DS, Burnham RS Botulinum toxin A versus bupivacaine trigger point injections for the treatment of myofascial pain syndrome: a randomised double blind crossover study.Pain. 2005;118:170-175.

[39] Fernández-de-las-Penas C, Svensson P. Myofascial Temporomandibular Disorder. Curr Rheumatol Rev. 2016;12:40-54.

[40] Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, Treede RD. A new definition of neuropathic pain. Pain. 2011;152:2204-5.

[41] Zakrzewska JM, Linskey ME. Trigeminal neuralgia. BMJ. 2015 Mar 12;350: h1238.

[42] Nurmikko TJ, Eldridge PR. Trigeminal neuralgia – Pathophysiology, diagnosis and current treatment. Br J Anaesth 2001;87:117-132.

[43] Sharav Y, Benoliel R, Schnarch A, Greenberg L. Idiopathic trigeminal pain associated with gustatory stimuli. Pain. 1991;44:171-4.

[44] Spencer CJ, Neubert JK, Gremillion H, Zakrzewska JM, Ohrbach R. Toothache or trigeminal neuralgia: treatment dilemmas. J Pain. 2008;9:767-70.

[45] Bowsher D. Treigeminal neuralgia. A symptomatic study of 126 successive patients with and without previous interventiokns; Pain Clinic 2000;12:93-98.

[46] Di Stefano G, Truini A, Cruccu G. Current and innovative pharmacological options to treat typical and atypical trigeminal neuralgia. Drugs. 2018;78:1433-1442.

[47] Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G.Trigeminal neuralgia - diagnosis and treatment. Cephalalgia. 2017 Jun;37(7):648-657.

[48] Renton T, Yilmaz Z. Profiling of patients presenting with posttraumatic neuropathy of the trigeminal nerve. J Orofac Pain 2011;25:333-344.

[49] Baad-Hansen L, Leijon G, Svensson P, List T. comparison of clinical findings and psychosocial factors in patients with atypical odontalgia and temporomandibular disorders. J Orofac Pain 2008;22:7-14.

[50] Baad-Hansen L, Benoliel R. Neuropathic orofacial pain: Facts and fiction. Cephalalgia. 2017;37:670-679.

[51] Haviv Y, Zadik Y, Sharav Y, et al. Painful traumatic trigeminal neuropathy: An open study on the pharmacotherapeutic response to stepped treatment. J Oral Facial Pain Headache 2014;28: 52–60.

[52] Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurol 2015;14:162–173.

[53] Benoliel R, Gaul C. Persistent idiopathic facial pain. Cephalalgia. 2017 Jun;37(7):680-691.

[54] Forssell H, Tenovuo O, Silvoniemi P, Jääskeläinen SK. Differences and similarities between atypical facial pain and trigeminal neuropathic pain. Neurology 2007; 69:1451–1459.

[55] Lang E, Kaltenhauser M, Seidler S, Mattenklodt P, Neundörfer B. Persistent idiopathic facial pain exists independent of somatosensory input from the painful region: Findings from quantitative sensory functions and somatotopy of the primary somatosensory cortex. Pain 2005;118: 80–91.

[56] Beecroft EV, Durham J, Thomson P. Retrospective examination of the healthcare 'journey' of chronic orofacial pain patients referred to oral and maxillofacial surgery. Br Dent J 2013;214 :E12.

[57] Zakrzewska J. Chronic/Persistent Idiopathic Facial Pain. Neurosurg Clin N Am. 2016;27:345-51.

[58] Weiss AL, Ehrhardt KP, Tolba R. Atypical Facial Pain: a Comprehensive, Evidence-Based Review. Curr Pain Headache Rep. 2017 Feb;21(2):8.

[59] Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211.

[60] Benoliel R, Elishoov H, Sharav Y. Orofacial pain with vascular-type features. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997 Nov;84(5):506-12.

[61] Silberstein SD, Holland S, Freitag F et al. Evidence-based guideline update : Pharmacologic treatment for episodic migraine prevention in adults : Report of the Quality Standards subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78:1337-1345.

[62] Dodick DW, Rosen TD, Goadsby PJ, Silberstein SD. Cluster headache. Cephalalgia 2000;20:787-803.

[63] Rozen TD, Fishman RS. Cluster headache in the United States of America : Demographics, clinical characteristics, triggers, suicidality, and personal burden. Headache 2012;52:99-113.

[64] Tfelt-Hansen PC, Jensen RH. Management of cluster headache. CNS Drugs 2012; 26:571-580.

[65] Osman C, Bahra A. Paroxysmal Hemicrania. Ann Indian Acad Neurol. 2018; 21(Suppl 1):S16-S22.

[66] Arca KN, Halker Singh RB. SUNCT and SUNA: an Update and Review.Curr Pain Headache Rep. 2018 Jun 21;22:56.

[67] Sharav Y, Benoliel R. Acute orofacial pain. In : Sharav Y and Benoliel R. Orofacial pain and headache; 2nd Ed. Chicago, Quintessence Publ Co, 2015, pp. 176-177.

[68] Then KL, Rankin JA, Fofonoff, DA. Atypical presentation of acute myocardial infarction in 3 age groups. Heart and Lung 2001;30:285-293.

[69] Kreiner M, Okeson JP, Michelis V, Lujambio M, Isberg A. craniofacial pain as the sole symptom of cardiac ischemia : a prospective multicenter study. J am Dent Assoc 2007;138:74-79.

[70] Jalali N, Vilke GM, Korenevsky M, Castillo EM, Wilson MP. The tooth, the whole tooth, and nothing but the tooth: can dental pain ever be the sole presenting symptom of a myocardial infarction? A systematic review. J Emerg Med. 2014;46:865-72.

[71] Kreiner M, Falace D, Michelis V, Okeson JP, Isberg A. Craniofacial pain of cardiac origin is associated with inferior wall ischemia. J Dent Res 2010;89:965-969.

[72] Yatani H, Komiyama O, Matsuka Y, Wajima K,Muraoka W, Ikawa M, Sakamoto E,De Laat A, Heir GM. Systematic review and recommendations for nonodontogenic toothache. J. Oral Rehabil. 2014;41:843-852.

[73] Walden A, Parvizi N, Tatla T. Toothache : an unlikely presentation of secondary breast malignancy. BMJ Case Rep 2011;16:2011.

[74] Hallock A, Rodrigues G. Toothache as a presenting symptom of metastatic renal cell cancer. Can Urol Assoc J. 2009;3:E42-4.

[75] Zadik Y, Vainstein V, Heling I, Neuman T, Drucker S, Elad S. Cytotoxic chemotherapy-induced odontalgia : a differential diagnosis for dental pain. J Endod. 2010;36 : 1588-1592.