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Neuroplasticity, Central Sensitization and Odontogenic Referred Orofacial Pain

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Abstract

Patients presenting with referred dental orofacial pain are not rare in dental clinics. The most common cause for referred dental craniofacial pain is of odontogenic origin. An accurate diagnosis will depend on a comprehensive clinical exam and dental history review. For differential diagnosis, it is critical to consider both the odontognic and non-odontogenic etiology. Once a correct diagnosis is established, a proper treatment can be administrated by elimination of the etiology. We describe the updated mechanism for referred pain with neuronal plasticity and central sensitization theory. Through clinical cases, we elucidate how the diagnosis of odontogenic referred dental craniofacial pain is achieved, and the etiology is established. Because of its complex nature, odontogenic referred dental craniofacial pain can be misdiagnosed and patients may receive unnecessary procedures. Proper knowledge and strategy would help to achieve success in the diagnosis and treatment of odontogenic referred dental orofacial pain.

Introduction

Pain is unpleasant sensation perceived by patient in response to noxious stimulation, which is usually associated with actual or potential tissue injury. In acute pain, the intensity of pain usually reflects the severity of tissue injury and it serves as a warning sign for self-protection. While in chronic or sub-acute conditions, the perceived pain may not exactly reflect the location and severity of noxious stimulus or tissue injury [1,2]. The pain reported by patients could be originated from peripheral noxious stimulation or injury (nociceptive and inflammatory pain) and/or nociceptive nervous lesion, neuropathy or functional abnormality (central pain, neuropathic pain, projected pain or referred pain). In certain circumstances, patients can not exactly identify the location causing the pain or perceive the pain at a location other than the site of injury or receiving the painful stimulation, a phenomenon that pain is felt in a location distant from the actual source of the pain is called referred pain [3].

For dental orofacialpain it is a common scenario that the patient has difficulty precisely distinguishing the affected tooth or region causing the pain [2-4]. In a report based on dental emergency patients with posterior toothache, 89.8% of the patients presented with referred orofacial pain [5]. This observation suggests that referred craniofacial pain is prevalent in dental pain patients. Even though the referred craniofacial pain can be of non-odontogenic etiology, such as sinus infection or even heart ischemia, the most common cause for referred dental craniofacial pain is of odontogenic origin [5]. If patients present with both a toothache and craniofacial pain, typically patients can identify the source of pain as dental origin. In most cases patients knew the primary occurred tooth pain causing their secondary craniofacial pain. While in some cases, patients may find the craniofacial pain is overwhelming compared to any tooth pain and only seek care for their craniofacial pain [5,6]. In a retrospective study, 17.2% of patient suffered from orofacial pains are odontogenic origin [7]. Odontogenic referred dental craniofacial pain is usually originated from injury, inflammation of dental pulp and/or periodontium including the gingiva [8-10]. Odontogenic referred craniofacial pain can be in a wide array of craniofacial pain manifestations, which include toothache [5], sinus pain, ear pain [5,6,11], facial pain [7], forehead pain and headache [3], jaw pain [7], temporalis and joint pain [3].

Mechanisms for Generation of Referred Pain

Referred pain is perceived at a location that is different from the site receiving the noxious stimulation. Experimental studies have demonstrated several unique characteristics of referred pain [12,13]. The referred pain is always secondary to the original stimulation (pain) i.e. there is a time delay before the appearance of referred pain. In order to induce the referred pain, it usually needs stronger stimulation than that for the original pain. Temporal summation of the original stimulation facilitates the appearance of referred pain. In addition, the somatosensory modality changes may also occur in the referred region, which suggest that neuronal plasticity or sensitization occurs during the development of referred pain. Several mechanisms regarding the generation of referred pain have been proposed.

Convergent-projection theory is one of the earliest proposed mechanisms for generation of referred pain. It stated that sensory afferent nerve fibers from different sites of the body converge onto the same nociception neurons in spinal cord or brain stem, and then send same pain signal to the cerebral cortex. Anatomic evidence has shown that sensations from the original and referred pain sites encoding to the same segment of the spinal cord [14]. Functional experimental study also demonstrated that referred pain depends on the intensity of stimulation that induces the original pain [14,15]. This theory can explain that jaw (muscle) pain can be referred to the teeth, and vice versa the tooth pain can also be referred to the jaw muscles [12]. However, this convergent-projection theory cannot explain the delay between the onsets of referred pain and the original pain stimulation. Experimental evidence also shows that referred pain and original pain is often a one-way relation, i.e. stimulation of the referred site, usually does not induce pain in the original site [12].

The convergence facilitation theory stated that somatosensory non-nociceptive afferent inputs provide facilitating effect on the generation of referred pain by creating "an irritable focus". This irritable focus enables noxious stimuli from other sites to be perceived as referred

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pain. Recently this theory has regained attention under the mechanism of central sensitization [16]. It proposed that central sensitization occurs as the neuronal circuits become more responsive after receiving repeated nociceptive stimulation. In central sensitization, the innocent or weaker noxious stimulus can trigger the referred pain. Recently, it has been observed that the spinal dorsal horn contains a silent circuit contains excitatory interneurons expressing PKC-γ [16]. This circuit is normally inactive because of receiving input from inhibitory glycine interneurons, but is activated under central sensitization [17,18]. This central sensitization-involved convergence facilitation theory provides a mechanism to explain the sensory modality changes observed in the referred region. It also can explain the delayed appearance of referred pain because of time required for the development of central sensitization [13]. However, it is difficult to explain that referred pain still remains after blocking the sensory inputs with local anesthesia in the referred regions.

The hyper-excitability theory proposed that in referred pain new receptive fields are created as a result of establishing new nociceptive afferent inputs in spinal cord dorsal horn or brain stem. This new nociceptive pathway can be achieved by activation of a latent inactive connections or generation of new synaptic connections to the secondary nociceptive neurons. Hyper-excitability occurs in the nociceptive neurons in central sensitization, which enable nociceptive neurons more efficiently receive nociceptive afferent inputs or even non-noxious stimulation inputs and send nociceptive signal to the brain [19]. It has been demonstrated that primary afferents and their central connections are capable of conducting significant modifications following axotomy and regeneration [20]. The nociceptive axonal terminal may sprout and form new synapses with the adjacent nociceptive neurons in spinal cord dorsal horn under certain neuronal insulting condition [21,22]. Besides establishing new synaptic connections, in central sensitization, activation of inactive connections in the spinal cord also occurred [23]. According to this theory, the pain signal from the original site could stimulate the adjacent nociceptive neurons that are responsible for the pain in the referred region. Therefore, central sensitization plays essential role for development of referred pain by establishing new afferent input to nociceptive neurons. Several characteristics are in line with this mechanism for referred pain, such as its stimulation-intensity dependency, the time delay for the appearance of referred pain and changes of the sensory modality in the referred pain region. In addition, this theory can explain the reamining referred pain after blocking the peripheral sensory afferent input in the referred pain region.

Even though there is no definitive consensus regarding the generation of referred pain, it is generally believed that the nociceptive neurons in spinal cord dorsal horn or brain stem can receive or can potentially receive convergent or overlapping inputs from different sites of the body. Therefore the brain cannot identify correctly the actual input sources. The referred pain mechanisms have been modified with concept of central sensitization [1,13,16]. It is believed that the neuronal plasticity changes in the dorsal horn or brainstem establish new nociceptive pathway to the nociceptive neurons. These plasticity changes play a central role for the development and maintenance of referred pain [12].

Odontogenic Referred Dental Orofacial Pain

Case 1

A 42-year-old Africa American woman visited Eastman Institute for Oral Health with multiple toothaches. The patient had experienced left maxillary and mandibular toothaches for 6 weeks and sought treatment two weeks ago. During her first visit the attending dentist suspected secondary caries that involved pulpitis and provided the option of endodontic treatment or extraction for patient. Amoxicillin and Ibuprofen were prescribed. The patient stated the prescribed antibiotics and analgesics did not relieve her pain. She reported that the pain was still present in her left maxillary and mandibular posterior teeth with a dull persistent aching quality. Temperature changes (cold and heat) exacerbated the pain. The condition became worse since her first visit and began to affect her sleep and daily activities. The patient denied temporomandibular joint (TMJ) pain during function and/or rest. She had difficulty pointing out the exact teeth that were bothering her.

Extra and intra-oral examination was unremarkable except for several missing teeth in the maxillary and mandibular dentition. X-rays demonstrated multiple restorations in the remaining teeth, but no cavity, periodontal/apical lesions or sinus related pathology were noted. Percussion demonstrated pain in tooth #12 (++), #13(+) and #17 (+). The cold test (Endo-ice) produced pain in teeth numbers #12 (+++), 13 (+) and 17 (+). Tooth #12 also displayed a lingering pain (>20s). The electronic pulp test (EPT) demonstrated all teeth on the left side were vital. Teeth #12, 13 and 17 displayed higher sensitivity than the other teeth in the quadrant. EPT induced longer lasting and more severe pain in tooth #12 (++). There was no obvious pain evoked when biting. After removal of the filling (#12), secondary caries and a tiny fissure on the central groove were noted. After local anesthesia to block the left maxillary superior posterior alveolar nerve (1 cartage, 2.0% Lidocaine with 1:100K Epinephrine), the patient reported that the pain in both the upper and lower teeth disappeared.

Extraction of tooth #12 was performed and the patient was dismissed with an analgesic prescription (Vicodin). The extracted tooth (#12) was re-examined and demonstrated the presence of micro fracture. One week after extraction, the patient reported that the pain in both upper and lower teeth disappeared. At the 4 weeks follow up, the response of #13 and #17 to cold tests become normal. No pain recurrence was reported.

Case 2

A 63-year-old Caucasian man sought treatment for periodic severe pain in his left upper jaw. The patient reported that his pain occurred couple times a day. This frequently occurred in the early morning when he woke up. Each time the pain lasted thirty minutes to 1 hour. The patient cannot identify factors that induce his pain. The patient is partially edentulous and has upper and lower dentures. The left upper maxilla is edentulous and shows no sign of inflammation or infection. No erythema, edema and ulceration were noted in the corresponding mucosa and gingiva. The patient reported discomfort on his left maxilla upon palpation but did not induce pain. Panoramic X-ray is unremarkable for left maxilla and mandible. There is gross decay in the left mandibular first molar (#19). Cold test induced lingering pain. The patient cannot recognize that the induced pain is exactly the same pain as he usually suffered. He also admitted he can not exactly figure out the origin of the pain he usually had. The decayed tooth (#19) was extracted under local anesthesia and the patient was dismissed with antibiotics and analgesics (Ibuprofen). In a follow up after two weeks, the patient reported that his periodic pain was gone and did not bother him again.

Case 3

An adult Caucasian male presented at the TMJ clinic seeking treatment for left facial and joint pain. The patient reported gradually developing continuous left face severe pain for 2 months. The intensity of the pain is about 6 to 8 on a scale of 0 to 10 visions. Some times, the

pain is intensified with cold, heat or chewing. Extra-oral examination was not remarkable. No swelling or asymmetric face was noted. Slight palpation pain was present in the left middle facial region. The patient has normal limits for mouth opening. No clicking and crepitation were noted in both sides of TMJ. X-ray showed no obvious changes in the condyle process of the TMJ. Intra-oral examination demonstrated a stained deep central groove in the occlusial surface of the mandibular molars. A fracture on tooth #18 was suspected. Lateral force was applied to the suspected tooth, which induced pain similar to the symptom of the patient previously sensed. Left infra-alveolar nerve blocking was performed, and the patient reported the TMJ pain is completely gone. More specifically, local anesthesia with intraperidontal ligament injection of tooth #18 on a second visit also abolished the TMJ pain. After extraction of the #18, the facial and TMJ pain disappeared.

The diagnosis and differential diagnosis in the above cases should include dental pulpitis, tooth microfracture, referred dental orofacial pain and central sensitization. However, other non-odontogenic etiology including atypical odontalgia, trigeminal neuroglia and neuropathies induced by other diseases or conditions need to be excluded. A careful review of dental history and comprehensive clinic examination/test are necessary to achieve a correct diagnosis. Concerning patient management, the following questions are raised in these cases (1), Are they odontogenic referred dental orofacial pain? (2) What is the initial and original etiology for causing this pain? (3) Are these conditions involved in neuronal central sensitization? (4) What clinical examination and tests are needed to produce a diagnosis? (5) What are the appropriate treatments for these cases?

Clinical Explanation

Dental pain patients usually have difficulty identifying the exact affected tooth or the pain source [2,4]. Dental pain patients usually present with referred orofacial pain [5]. In most cases, the patient can remember or identify the original site that causing the subsequent orofacial pain. However, as the time lapsed, the subsequent pain may overwhelm the original pain or the original pain might be ignored at the beginning. Some patients cannot identify the original site for the pain or even sought treatment only for the referred pain. Therefore, referred orofacial pain can be present with or without the original dental pain. In Case 1, the patient reported an original tooth pain in tooth #12, while in Case 2 and 3, no obvious pain was reported in the original sites by patients. Since the generation of referred pain is secondary to the original pain stimulation and there is usually a delay after original pain [15]. A detailed dental history review is helpful for conducting an accurate diagnosis of odontogenic referred pain.

The symptoms and illness history reported in Case 1 indicate that the pain in tooth #13 might be due to the infection (either periodontal or pulpal origin) or traumatic injury in #12. During embryo development, the trigeminal ganglia neuron axon growth and innervation of their peripheral targets is prior to the development of the orofacial tissues [24,25]. It has been shown that the trigeminal nerve fibers reach the embryonic mandibular and maxillary process by establishing an initial diffuse target field innervation patterns [24-26]. In deed, overlapping of axonal terminal innervation in adjacent teeth dominates within the same quadrant [27]. It is plausible that the noxious stimulation present in tooth #12 stimulates the nerve fibers that also innervate #13. Since the posterior regions of the maxillary and mandibular are originally adjacent during the embryonic development, overlapping innervation between upper and lower jaws may also present. Therefore, refereed pain also occurs in upper and lower opposite quadrant teeth, while referred pain is seldom observed in opposite quadrant teeth across the midline. This is also demonstrated in Case 1 that the problem in tooth #12 also induced referred pain in #17.

Beside the existence of axonal innervation overlapping, the convergent projection theory provides interpretation for much far away distance between original stimulation site and the referred pain location, which can explain dental pulpitis in tooth #19 induced refereed pain in the left quadrant maxilla in Case 2 and the micro-fractured tooth in #18 induced left TMJ/ facial pain in Case 3 respectively. Similar to the process of peripheral target innervation, the axonal growth and innervation of trigeminal ganglia neurons to their central targets (the secondary nociceptive neurons) in the brain stem is also a diffuse pattern [26]. As different orofacial tissues are developed, this initially diffuse target field innervation patterns is gradually transformed to a more precise topographical mappings in the nervous system [26]. In the adult, the inappropriate connection is eliminated by neuronal apoptosis or is inactivated by functional modification, and favorable connection is consolidated. However, in referred pain condition (central sensitization) the activation of the inactive connection or re-establishing of previous diffuse connections may provide convergent projection from different orofacial tissues to the nociceptive neurons in the brain. Interestingly, electrophysiology studies have demonstrated that stimulations from different oral facial tissues induce responses in the same segment sensory neurons in the brain stem [15].

Referred pain is evoked by the original noxious stimulation and usually depends on the intensity of the stimulation [14]. In order to confirm the odontogenic referred pain it has been recommended to check if applying original stimulation to the suspected tooth or teeth can induce hyper-reactive response in the referred site. Indeed, when stimulation of either cold (Case 1, Case 3) or mechanical force (case 3) is applied to the suspected tooth, hyper-reactivity pain response similar to the reported referred pain was induced in these cases. Since the referred pain depends on the noxious stimulation in the original site, local nerve blocking anesthesia would be a powerful tool to distinguish the original noxious stimulation site and the referred pain site. As expected, when local anesthesia was given to block the tooth with referred toothache of #17 (Case 1), the patient still felt the pain. While as the local anesthesia was delivered to the tooth #12 (original site), the referred pain was totally abolished in the same case. Similar results were also achieved when the original pain teeth were anesthetized in Case 2 and Case 3. These results strongly suggest that blocking the noxious stimulation in the original site will abolish the referred pain. If the clinician still has trouble to localize which tooth is causing the pain, especially in the same quadrant, as demonstrated in Case 3 a periodontal intraligamental injection to the susceptible tooth should be performed. It was furthermore confirmed that after extraction of the suspected teeth, the referred pain disappeared in all the cases.

Patients with chronic referred pain might be accompanied with psychological and emotional changes. Sometimes it is difficult to make an accurate evaluation and specific diagnosis for the referred pain. Another reason that makes the situation more complicated is development of pain sensitization [16,28]. Pain sensitization is characterized with plasticity changes in the nociceptive neuronal circuits that occur in both the peripheral and central nervous system. These changes can be involved in the regulation of nociceptive receptors, ion channels, presynaptic vesicle release, postsynaptic receptors accumulation induced by cytokines, inflammatory factors, neuronal transmitters and even the pain signal itself [16]. Astrocytes and other immune cells also participate in the process of pain sensitization [1]. The consequence of pain sensitization is the presence of hyperalgesia, allyodenia in the affected regions. The patients become more sensitive

to noxious stimulation (hyperalgesia) or even feel pain to innocuous stimulation such as slight touch [1] or gentle percussion in the affected teeth (allyodenia).

The current theory believes that pain sensitization is accompanied with and attributed to the generation and maintenance of referred pain [16]. Central sensitization can explain why the referred pain teeth (sites) display sensitivity in response to percussion, cold or electric stimulation in teeth #13 and 17 in Case 1 and the palpation pain in the affected TMJ in Case 3. Central sensitization can also induce the sensory modality changes in the referred pain region, which can explain the uncomfortable sensory changes in the maxilla in Case 2 while gently palpation was applied to the affected region.

Principles for Diagnosis and Management of Odontogenic Referred Orofacial Pain

Most referred dental orofacial pian are odontogenic origin [5]. Howver, referred dental orofacial pian can also arised from TMJ disorders, myofascial pain, sinus problem, or even cardiac infarction [2]. The referred dental orofacial pain is different from the projected nerve pain, which is felt throughout the peripheral distribution of the affected nerve (trigeminal neuralgia, cluster headache, post herpetic neuralgia etc.). The referred orofacial pain is also different from pain radiation, a severe tooth radation pain may radiate to the whole jaw, the head, neck or the shoulde. For differential diagnosis, other non-odontogenic referred dental orofacial pain should be considered [2,29-32].

Dental practitioners should be aware of the complex mechanism of referred pain and the manner in which teeth and other orofacial structures may simulate the referred dental orofacial pain. The odontogenic referred dental orofacial pain should be distinguished from the neuropathic pain, idiopathic pain, neurovascular pain and psychogenic pain or pain of psychosocial origin. The differential diagnosis should also include the possible pain caused by other various conditions or diseases, such as carcinoma metastasis in oral and maxillofacial area induced pain [33,34]. In addition, diabetes related or chemotherapy-induced peripheral neuropathy might manifest as pulpitis-like toothache [33,35]. Therefore, in patients who present with dental orofacial pain, dental practitioners should consider all the possible alternate etiologies of the pain when appropriate diagnostic tests cannot lead to odontogenic etiology. Failure to establish the etiology of the pain will result in incorrect diagnosis and inappropriate treatment. Therefore, a careful review of all the possible orofacial pain etiologies should always be considered for differential diagnosis of referred dental pain [2].

An accurate diagnosis for odontogenic referred dental orofacial pain depends on careful clinic exam and comprehensive dental history review [30]. Since the onset of the referred pain is always secondary to the original pain, present illness history review may provide clue for tracing the etiology of the referred pain. The development and maintenance of referred pain also depends on neuronal plastic changes induced by intensive and long-term noxious stimulation in central sensitization. Even though the referred pain may overwhelm the original pain and the patient just sought treatment for the subsequent pain, a detailed review of the dental illness history may help figure out the initial site that causing the subsequent orofacial pain.

For diagnosis of odontogenic referred dental orofacial pain, it is very important that the clinician identifies the offending tooth / teeth. Teeth with obvious fractures or rampant dental caries are easy to identify and treat. In many cases the source of tooth pain in a quadrant are difficult to identify, especially in bicuspids and molars. For fractured tooth, placing lateral difficult force on the cusps with a tooth slooth is often helpful. Sometimes it is difficulty to identify the fracture in the teeth below the gum line. X-rays are often negative for identifying microfractured tooth. Diagnostic tests are essential for the diagnosis of odontogenic referred orofacial pain. For dental pulpitis tooth, cold and hot stimulation is useful to identify the original affected teeth. Patients with root canals in one or multiple teeth, without pain relief, are also difficult to diagnose. If the tooth has a filling, the clinician may remove it and look for the crack with the help of dye staining or light illumination.

If it is difficult to identify which tooth/teeth is the cause, a local alveolar nerve blocking anesthesia test should be administered, which would be a useful way to identify the original stimulation site for referred pain in different quadrant. Alveolar nerve blocking may not be always effective to identify the offending tooth/teeth, especially for distinguishing the teeth in the same quadrant. Interligamentous administration of local anesthesia with a 30 gauge needle may aid in the identification of the problem tooth/teeth. This may have to be administrated on more than one occasion. Since the presence of central sanitization in referred pain, a sensory functional test will determine the presence of hyperalgesia and allodynia in the affected region, sensory modality changes may also present in both the original site and the refereed site. Therefore, a quantity sensory test would be a useful assay for the diagnosis of referred pain.

An exploring treatment is suggested only for extremely difficult cases. Before establishing a diagnosis for odontogenic referred orofacial pain, any treatment especially for aggressive and traumatic procedures such as extraction, endodontic treatment , apicoectomy and periodontal surgery should be avoided [28]. It is suggested that a conservative treatment is always the primary consideration. If no appropriate diagnosis was achieved, a referral to other specialists is recommended.

For treatment of referred dental orofacial pain, it is usually a straightforward strategy. Once the original source of the referred pain is identified and the etiology of diagnosis is established, the treatment is to eliminate the cause for the pain. However, in some conditions such as in the case of phantom pain or atypical odontalgia (AO), it is not easy to figure out the original site and cause of the pain, which make sthe diagnosis and treatment for referred dental orofacial pain more challenging. Prevention and control of pain is crucial for cases with uncertain origin of the pain, which can prevent the development of central sensitization and reduced the incidence of worsening condition. Further study for the mechanisms of referred pain and central sensitization is required to better understand, assess and treat the referred dental orofacial pain.

In summary, a comprehensive clinical examination and careful review of the present illness history help to reveal the nature etiology of pain. Local stimulation and anesthesia is a useful tool for the diagnosis and differential diagnosis of odontogenic referred orofacial pain. It is crucial to make a correct diagnosis and identify the original source of the pain [2]. The efficient way to relieve referred pain is to eliminate the original cause for the pain.

Conclusions

The clincal cases described here fulfill the diagnostic criteria for referred orofacial pain, which are evoked by the presence of odontogenic etiology. If the pain has lasted for long time, it is likely that neuronal plasticity and central sensitization had developed. Central sensitization, which is characterized with the presence of hyperalgesia

and allyodenia, made the diagnosis for referred dental orofacial pain more difficult. An accurate diagnosis depends on a comprehensive examination and careful dental history review. Referred dental orofacial pain should be differentiated from trigeminal nerve neuropathy projected pain and other orofacial pain caused by various conditions or diseases, such as carcinoma, metastasis and chemotherapy neuropathy. An Exploring treatment is usually suggested for extremely difficult case. Before achieving a solid convincing diagnosis, any aggressive procedure should be avoided. In addition, preemptive analgesia including the use of analgesics and local anesthetics should be considered to prevent central sensitization and incidence of worsening condition. Once the diagnosis of odontogenic referred pain is established, the treatment is to eliminate the etiology causing the original pain.

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