

# Research Progress of Unexplained Headache and Potential Oral and Maxillofacial Diseases

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**Abstract:** Headache is a common nervous system symptom with complex causes, including neurogenic, odontogenic, vascular, infectious and so on. Headache is generally manifested as pain in the region above the skull, orbit and occipital bone. But sometimes it also involves pain in the oral and maxillofacial region, because the craniofacial region is closely adjacent to the oral anatomy. Some oral diseases, such as pulpitis, temporomandibular joint disorder syndrome, and oral mucosal disease, can not only cause pain at the primary site, but also show head and face pain. Therefore, headache is easily confused with some oral diseases in clinical diagnosis. A large number of clinical reports at home and abroad have analyzed the correlation between neurologic diseases and oral diseases. This paper attempts to analyze the internal relationship between the two from clinical manifestations, pathogenesis and other aspects, focusing on the discussion of headache caused by oral diseases, which is meaningful for stomatologists and neurologists, and is conducive to expanding the thinking of oral disease research and diagnosis and treatment.

**Keywords:** Headache, Pulpitis, Temporomandibular Disorders, Oral Mucosal Disease

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## 1. Introduction

The contemporary medical model attaches great importance to the quality of life of human beings, and headache, oral and maxillofacial pain can have a negative impact on the quality of life of people at all ages. Headache is a common nervous system symptom, while oral diseases generally refer to diseases occurring in the oral cavity. The two seem to be unrelated, but because the adjacent relationship between the head and face and oral anatomy is very close, there may be some internal relationship between the two. Headache can involve oral and maxillofacial regions, and odontogenic headache caused by oral diseases is not uncommon. Many clinical reports at home and abroad reported that odontogenic headache was misdiagnosed as migraine or angioneurotic headache. We should be careful in studying the causal relationship between neurological diseases and oral diseases, and should not draw conclusions prematurely. and this

relationship is significant for stomatologists and neurologists in the diagnosis and treatment of diseases. In this paper, pulpitis, temporomandibular joint disorder and oral mucosal disease, which are common oral diseases causing headache of unknown cause, are described. To provide more reference for clinicians to diagnose unexplained headache in oral diseases.

## 2. Pulpitis and Migraine

Pulpitis is the most common pulp lesion. It is a connective tissue inflammation, mainly caused by bacterial invasion and infection secondary to deep caries. Other causes include physical and chemical stimulation and immune response. The pulp is located in the pulp cavity, surrounded by hard dentin and has limited space. When pulpitis occurs, pulp inside angiectasis hyperemia, inflammatory exudate cannot receive timely drainage and gathered themselves together. Dental pulp cavity pressure increased, oppressive nerve leads to severe pain. At the

same time, the release of inflammatory medium pain by cell damage can act directly on the nerve endings. So when the onset of pulpitis, mainly for patients with severe toothache. The pain is characterized by spontaneous pain, paroxysmal pain, radiation pain, usually onset at night, stimulated or aggravated by hot and cold stimuli. According to relevant research, the formation of pulpitis pain mechanism consists of three conduction stages of pulp nerve, trigeminal ganglion, brainstem and ventral posteromedial nucleus of thalamus, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), adrenocorticotropin-releasing factor receptor (CRF), toll-like receptor 4 (TLR4), and voltage-gated ion channel 1.7 (Nav1.7), satellite glial cells (SGCs) and other molecules. Among them, Arora S *et al.* detected that the expression level of TNF- $\alpha$  was positively correlated with the level of pulpitis pain, and it was an important initiating factor in the process of inflammation [1]. TNF- $\alpha$  is secreted and produced by mononuclear macrophages. On the one hand, it chemotaxis leukocytes to migrate to inflammatory tissues, induces vasodilation and stimulates the production of pro-inflammatory cytokines to participate in the formation and maintenance of inflammation [2]. At the same time, TNF- $\alpha$  can also directly stimulate sensory neurons to increase the sensitivity of sensory nerves to pain [3, 4]. CRF may be dependent on opioid receptors and glucocorticoid receptors to produce analgesic effects in midbrain perihydrogenic gray matter [5]. The expressions of TLR4, Nav1.7 and SGCs in the spinal nucleus of trigeminal nerve were positively correlated with the degree of pulpitis pain.

The dental pulp has only pain receptors but no proprioceptor. The nerve of the dental pulp mainly comes from two branches of the trigeminal nerve: maxillary nerve and mandibular nerve. Pain often radiates along the area innervated by the maxillary and mandibular branches of the trigeminal nerve to the upper and lower jaw, face, ear and temporal parts of the affected side. So that it is difficult to determine the location of the affected tooth. This is also one of the important reasons why pulpitis is easily misdiagnosed as migraine. Migraine is a common neurological disease, mainly manifested as unilateral throbbing headache, accompanied by nausea, vomiting, sensitivity to light and sound, and aggravated pain during head movement [6]. Migraines can also involve the face and mouth, and are prone to confusion from odontogenic headaches caused by pulpitis. Most of the patients with odontogenic headache have obvious toothache symptoms. Headache is only one of the accompanying symptoms, patients first diagnosed in the department of stomatology, generally will not be misdiagnosed. However, there are sometimes patients with odontogenic headache who have no obvious symptoms of toothache or only present as paroxysmal headache. The paroxysmal nature of pulpitis and the fact that pain can radiate to the temporal part of the affected side of the head are similar to migraines, so pulpitis without obvious toothache symptoms is easily misdiagnosed as migraine. Especially when the patient denies a history of toothache, neurologists know little about oral diseases, and there are no positive signs on neurological examination. Therefore, it is easy to misdiagnose pulpitis without obvious

toothache symptoms as migraine. Clinical cases of pulpitis with headache as the first or main symptom have also been reported. In addition, when the caries location is hidden and the teeth and pulp stones are hidden, there are no obvious clinical symptoms in the early stage, and the affected teeth do not have any positive signs. The pulp stones keeps increasing and oppresses the pulp nerve, thus causing long-term radiation pain in the head and face, which is difficult to diagnose and often delays the treatment time [7].

### 3. Temporomandibular Joint Disorder Syndrome and Cervicogenic Headache

Temporomandibular joint disorder syndrome (TMJDS), also known as the temporomandibular joint disorders (TMD), is a general term for a group of diseases that involve the temporomandibular joint and/or masticatory muscles and have the same or similar clinical symptoms. TMD patients are often accompanied by temporomandibular joint pain, temporomandibular joint clicking and mouth opening limitation. TMD is a common jaw and stomatological disease. In fact, TMD is very common. Studies have shown that the prevalence of TMD in some populations can be as high as 75%, and about 33% of the population show one or more symptoms of the disorder [8]. The main site of pain caused by TMD is the temporomandibular joint area, but sometimes it can involve the temporal, ear, half of the masticatory muscles, and even lead to half of the headache. Headaches caused by TMD are usually unilateral and are often located in the perioral area, and the movement of the masticatory muscles usually exacerbates this pain. TMD is more common in patients with muscle dysfunction, especially molar and incisor tooth wear. [9]. There is evidence that headache due to TMD may be closely related to cervical headache (CEH), and although cervical spine dysfunction is an important contributing factor to CEH, some authors have suggested that temporomandibular disorder (TMD) may also be a contributing factor to the onset of CEH in some patients. There is no doubt that there is a close anatomical, functional and pathophysiological relationship between cervical spine and TMD. Piekartz [10] believes that the pathogenesis of TMD-induced CEH may be due to the influence of TMD dysfunction on cervical spine. Pain caused by TMD may cause sensitivity of the cervical nucleus of trigeminal nerve, and local sensory sensitivity and the decrease of nociceptor threshold will further lead to cervical spine injury, which can lead to CEH. It is generally believed that the injury of C1-C3 high nerve roots and/or their innervating tissues is the anatomical basis of CEH. When C1-C3 nerve roots are subjected to compression or inflammatory stimulation, the nociceptive information caused by the lesions of the upper cervical nerve pathway will converge in the central center, resulting in referred pain of the head and face [11]. Greenbaum believed that TMD caused headache because of overlapping innervation of the trigeminal nerve [12]. Up to now, the mechanism of TMD triggering CEH has not been

fully elucidated by the academic circle. But it is clear that there is a close relationship between TMD and CEH in the past. The diagnosis of TMD is usually made by clinical examination and listening to the voice of temporomandibular joint. In addition, there are some indicators of disorders, such as jaw offset, maximum jaw opening, jaw locking, etc. [13]. It is not difficult to make a diagnosis based on the typical clinical manifestations of TMD patients. However, due to the correlation between TMD and CEH, clinicians should treat TMD as soon as possible after diagnosis to avoid further development of TMD resulting in cervical injury and CEH, which will bring more trouble to patients.

## 4. Oral Mucosal Disease and Headache

### 4.1. Burning Mouth Syndrome (BMS)

Burning Mouth Syndrome (BMS) is a group of syndromes characterized by burning pain of oral mucosa, which is also known as tongue pain [14]. It is often accompanied by dry mouth and paresthesia, but there is no organic disease of the mouth and mucous membrane damage [15]. Migraine is a common chronic neurovascular disease, mainly manifested as unilateral throbbing headache, pain sites including craniofacial, lip, tongue, easy to be confused with BMS. According to relevant studies, the view that migraine and orofacial pain are closely related has been recognized [16]. In terms of pathogenesis, the etiology of BMS is still unclear, but current studies have found that its pathological mechanism is related to the central and peripheral nervous system, which is due to the changes of small C-type nerve fibers of trigeminal nerve sensors and abnormal secretion of neuropeptides in saliva. A large number of studies have shown that the pathogenesis of migraine is closely related to trigeminalvascular system (TGVS), and the activation of TGVS is the key to the pathogenesis of migraine [17]. Stimulating the trigger migraine starting point, in vivo and in vitro in cortical spreading depression (corticalspreadingdepression, CSD), trigeminal nerve sensitization, activation TGVS, this results in the release of vasoactive substances such as calcitonin gene-related peptide (CGRP) from trigeminal nerve endings. CGRP mediates TGVS signal transduction through a series of cascade reactions, leading to degranulation of mast cells in the dura mater and neurogenic inflammation, promoting vasodilation, activating trigeminal pain-sensitive neurons in the dura mater and intracranial vessels, and triggering migraine [18]. It can be seen that there are abnormal trigeminal nerve fibers in both BMS and migraine patients.

### 4.2. Melkersson-Rosenthal Syndrome (MRS)

Melkersson-rosenthal syndrome (MRS) is a rare non-caseous granulomatous disease characterized by the triad of recurrent oro-facial swelling, recurrent facial palsy and tongue cleft (wrinkled tongue), which is a common cause of recurrent peripheral facial palsy [19]. In addition to the typical triad of MRS, recurrent craniofacial

autonomic nervous system symptoms can also occur, including headache, migraine, auditory hypersensitivity, abnormal saliva secretion, facial sensory retardation, etc. [20]. Foreign researcher Rozen once reported a case of persistent headache caused by MRS, which was relieved after dapsone treatment for the primary disease [21]. The mechanism of MRS causing headache is still unclear. This phenomenon may be caused by MRS symptoms compression of the facial nerve [22]. Some scholars also believe that MRS may cause local neurological symptoms similar to migraine or directly cause migraine by affecting trigeminal nerve function or other cranial nerves. Clinically, the characteristics of headache caused by MRS are highly similar to migraine. So attention should be paid to differential diagnosis and treatment.

## 5. Conclusion

The above is a tentative analysis of the relationship between headache and oral diseases. The causes of headache are very complex. The headache caused by nervous system diseases may involve the oral and facial areas, but the headache factors caused by oral diseases are often ignored and mistaken for diseases of the nervous system. The characteristics of radiation pain in pulpitis make it easy to be misdiagnosed. The close anatomical, functional and pathophysiological relationship between TMD and cervical spine makes it important for clinicians to correct TMD as soon as possible after the diagnosis of CEH. Oral mucosal diseases such as BMS and MRS have similar abnormalities of trigeminal nerve or facial nerve fibers to migraine, so they are easily confused with migraine. Clinicians should not make early conclusions when diagnosing neurologic diseases, and should carefully identify whether there are oral diseases. so that relevant treatment methods can be used as soon as possible to alleviate the headache symptoms of patients.

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