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Case Report

THE MIGRAINE-VERTIGO-PERIODONTAL DISEASE CONNECTION: EVIDENCE-BASED CASE AND VERIFICATION IN AN ANIMAL STUDY

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ABSTRACT

Recently, two CNS disorders, migraine and anxiety have been recognized as being commonly associated with dizziness (Vertigo). These associations may be an expression of an etiological relationship, for example, dizziness caused by migraine, or dizziness caused by anxiety and termed as MARD. Chronic dizziness may become more disabling during the added stress of a migraine headache or panic attack. In addition, dizziness occurred comorbidly with both migraine headache and anxiety disorders. Even though the etiology of migraine had been suggested from trigeminal nerve sensitivity and neurogenic inflammation, its linking to periodontal disease that innervated by the same nerve was still uncertain. However, an animal study revealed that Porphyromonas gingivalis lipopolysaccharide stimulation was able to increase neurogenic inflammation. A male patient suffered with symptoms mimicking MARD for years and concomitantly had chronic periodontitis. Scaling and root planning combined with the assisted drainage therapy resulted in instant disappearing of most of the symptoms. This case report is to propose the mechanism of periodontal disease involvement in the etiopathogenesis of migraine and vertigo which could be treated with periodontal treatment. Regarding to remarkable result, it was concluded that periodontal disease could be a source of neurogenic and immunogenic inflammation which if not treated periodically could perpetuate symptoms mimicking MARD.

Key words: *periodontal disease, migraine-anxiety related dizziness*

INTRODUCTION

Migraine-anxiety related dizziness (MARD) is a new term proposed by Furman *et al*.[1] for a disorder which related to the co-morbidity of migraine, anxiety and dizziness (vertigo).The existing link between migraine and balance disorders and the link between anxiety and balance disorders suggests that a subgroup of such patients will manifest migraine, anxiety, and a balance disorder at the same time. Treatments of MARD were depended to the predominance and the treatment phases of the symptoms. The predominant symptoms could be vestibular (i.e Meclizine), migraine (i.e Triptan) or anxiety (i.e. Clonazepam). The treatment phases of the symptoms were acute, preventive and maintenance.[1,2]

The possible link between oral focal infection and non-oral diseases had been studied by Li *et al*.[3] based on the evidence-based case reports. In addition, several case reports revealed that elimination of oral focal infection had beneficial effects to sinusitis[4] and headache[5,6] and symptoms mimicking Chronic Fatigue Syndrome (CFS).[7] However, studies related to the link between periodontal disease and the etiopathogenesis of MARD is still unclean. The successful result of periodontal treatment for MARD symptoms is beneficial for minimizing drug abuse.

A disorder which also had similar symptoms as MARD is Chronic Fatigue Syndrome (CFS). Chronic fatigue syndrome (CFS) is the current name for disorders characterized by debilitating fatigue and several associated physical, constitutional, and neuropsychological complaints which lasting more than 6 months and coupled with 6 or more arbitrary symptoms.[8,9]

There are various symptoms that frequently suffered by CFS patient i.e. difficulty in concentrating, headache, forgetfulness, sore throat, muscle aches, tender lymph nodes, feverishness, sleeping disturbances, psychiatric problems, allergy, dizziness, abdominal cramps, rapid

pulse, chest pain, night sweats, palpitations, premenstrual syndrome (PMS) etc.[9,10]

Studies on stress-associated disorder or immune dysregulation have interested scientist and clinicians in the field of psychoneuroimmunology (PNI). The field focuses on the interactions among central nervous system and the immune system, and the impact these interactions have on health.[11] It is also interesting that stress impaired periodontal disease.[12]

A possible correlation of oral focal infection with MARD could be predicted regarding to an object observation of a phenomenon that related to symptoms mimicking MARD. Scaling and root planning (SRP) that had been conducted to a male patient suffered from symptoms mimicking MARD was able to relief all of the symptoms. Moreover, recent study by Utomo[13] revealed that *Porphyromonas gingival*is lipopolysaccharide (*Pg*LPS) stimulation increased neurogenic inflammation, via increasing the substance P (SP) and calcitonin gene-related peptides (CGRP) that had a correlation with migraine.[14] In this study, the "assisted drainage therapy", a modification of SRP which including massage of the subgingival tissue, was able to decrease systemic CGRP level in minutes.[13]

The purpose of this case report is to reveal the possibility of the periodontal disease involvement in the etiopathogenesis of MARD, based on the remarkable result of scaling root planning and the assisted drainage therapy to a patient suffered from symptoms mimicking MARD. However, further researches should be done to support the validity of this successful clinical evidence-based case treatment.

CASE

A 44 years old male patient came to the dental clinic in the Faculty of Dentistry Airlangga University Surabaya, after reading about the connection between dental and systemic diseases in a local media. He suffered from several symptoms such as vertigo, headache, fatigue, pain and spasms of the neck and shoulder muscles, palpitations and blurred vision.

The illnesses started two years earlier, he was a very active individual who spent most of his time traveling by plane to other islands in Indonesian archipelago. During the journey, he often experienced the sensation of falling down, dizziness, heart palpitation and sometimes he felt as if his heart stopped for a while. These symptoms made him afraid of travelling by plane.

Treatment and medications had already been conducted by general practitioner, internist and cardiologist. Several diagnostic procedures have been done, such as chest x-ray, Electrocardiography (ECG) and treadmills, the results were all normal. The results of blood laboratory tests and urinalysis were mostly normal except for total cholesterol and LDL cholesterol.

There were a lot of prescribed drugs such as, sodium diclofenac (NSAID), meloxicam (COX2 inhibitors), tizanidine-HCl (muscle relaxant), lecithin (liver function supplements), cinnarazine (anti vertigo), flunarizine (drug for migraine, cerebral and peripheral equilibrium disturbances), vitamins B and E, lanzoprazole (drug for gastric and duodenal ulcer), chlordiazepoxide + clinidium (anti-anxiety), clobazam and alprazolam (tranquilizer), bisoprolol fumarate (anti-hypertensive, angina pectoris) and acetyl salicylic acid (as an anti-coagulant).

From physical examination, despite his stressful face, extra oral were normal, intra orally there were a lot of calculus deposits and gingivitis noted in all regions (Fig. 1 and Fig. 2). Probing revealed that deep periodontal pockets (5–7 mm) existed in every region, especially in posterior teeth (Fig. 3). No caries was found.

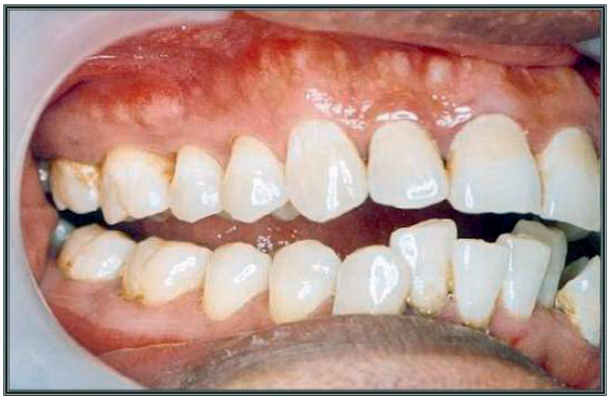

Figure 1. Intra oral, right side.

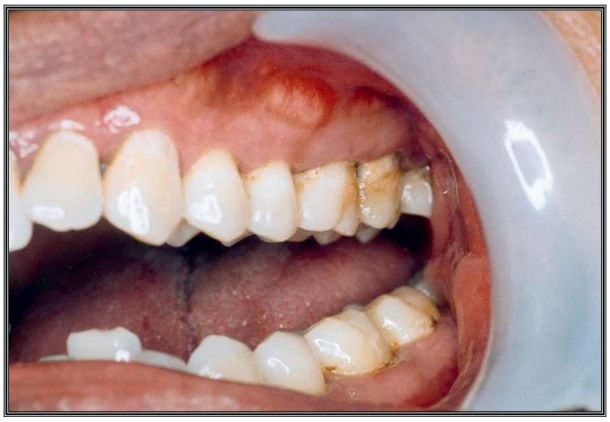

Figure 2. Intra oral, left side.

CASE MANAGEMENT

Visit #1 Scaling and root planning with piezoelectric scaler was conducted, followed by the assisted drainage therapy. It consisted of SRP with sickle-shaped scaler which simultaneously massaging the subgingival area for about 2–3 minutes (Fig. 4 and Fig. 5) in the left regions, because

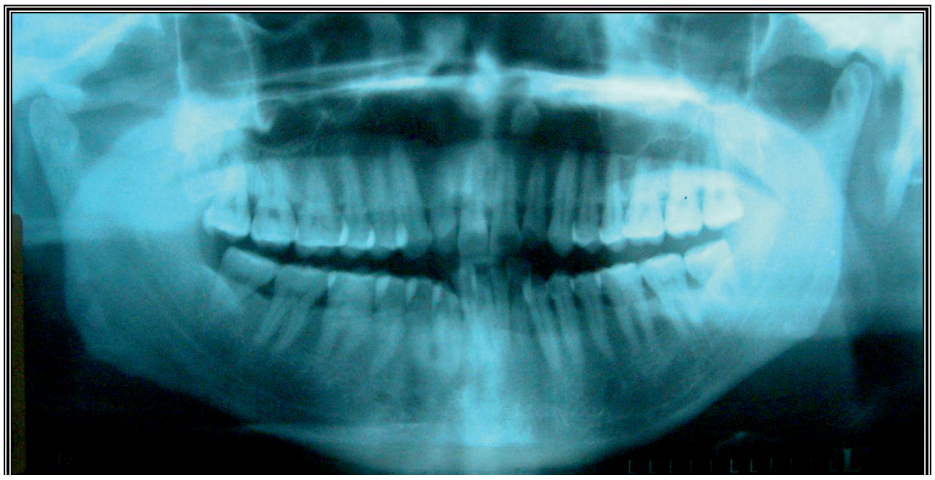

Figure 3. Panoramic radiograph.

the patient felt that the left side had the worst symptoms i.e. headache and neck muscle spasm.

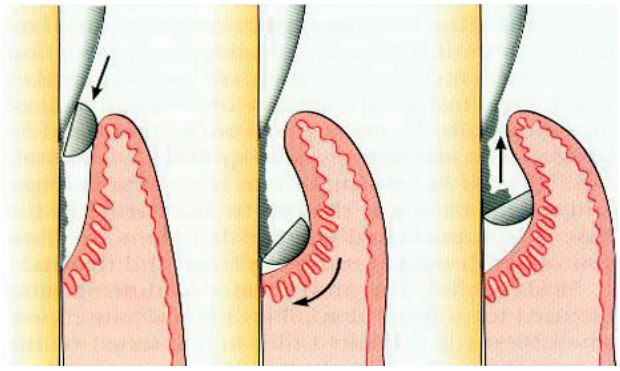

Figure 4. The assisted drainage therapy, scaling-root planing (SRP) combined with subgingival massage (red arrow).[15]

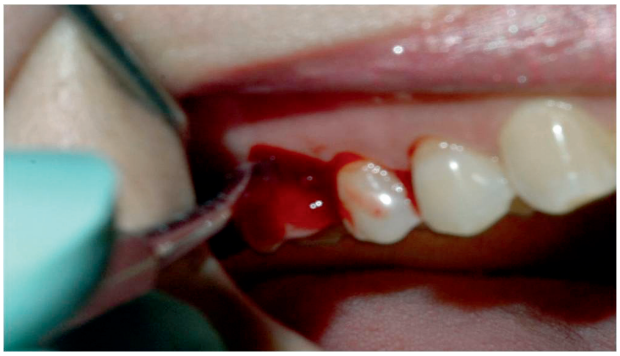

Figure 5. The assisted drainage therapy in patient.

Subsequently, in a few minutes after the periodontal treatments, the patient had already experienced a significant difference. He was able to stand without afraid of falling down; it could be from the diminished headache and vertigo symptoms. Then he was scheduled for the next visit three days later, nevertheless it was cancelled since he had been flown to Denpasar.

Visit #2. Ten days later, the patient felt more comfortable, headache and vertigo symptoms and the heart palpitation were disappeared. The same periodontal treatments were done in the right regions. Several minutes later the patient felt more comfortable and according to him, his eyes could see clearer than before, and amazingly, he was able to read without glassed, before that he had to wear (+) 2 eyeglasses. Several days later, after examining his eyesight, his opticians confirmed that this result was true.

Visit #3. One week after visit #2, all symptoms were disappeared, he had been gone to Irian several days before which supported the successful result of the periodontal treatments to the mimicking MARD symptoms. At that time, selective grinding was conducted in order to eliminate traumatic occlusions, and to facilitate smooth anterior and lateral mandibular movements. After this procedure, the patient felt more comfortable. Patient was expected to have his periodontal health checked every 6 months.

Evaluations were done one year later and the following six months, the symptoms did not reappear

DISCUSSION

According several literatures and studies, periodontal treatment and the assisted drainage therapy were able to reduce or eliminate several symptoms such as headache, sinusitis, fatigue, muscle pain or spasms[4,5,7] and asthma.[13] Even though the etiopathogenesis is still unclear, the same result also occurred in this patient, who had no more dizziness and followed by diminish of headache after the treatment and also heart palpitations several days later.

Oral focal infection such as periodontal diseases were able to elicit systemic infection and modulate systemic immune response.[3,15] One of the systemic effects of infection is sickness behavior; it refers to the coordinated set of behavioral changes that develop in sick individuals during an infection. At the molecular level, these changes are due to the effects of local pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α

(TNF-α) which may also affected the brain if produced in sufficient concentration.[16,17]

The cytokine-induced sickness behavior symptoms such as fatigue, malaise, headache, sleep disturbances, inability to concentrate and other symptoms are due to the brain action of pro-inflammatory cytokines[17,18] and nitric oxide (NO) which is produced by inflammation and infection.[19] In addition, CFS is closely related with cytokine-induced sickness behavior.[16,17] There is a possibility that MARD also related to cytokine-induced behavior. Nevertheless, to distinguish from a CFS patient, at least serum cortisol level should be measured.[9,10]

Bacterial endotoxins (lipopolysaccharides, LPS) are part of outer cell wall of Gram-negative bacteria. Lipopolysaccharide challenge upregulates the expression of endothelial cells adhesion molecules-1 and stimulate the release of high levels pro-inflammatory mediators by macrophages or monocytes such as IL-1β, IL-6, TNF-α, prostaglandin E2 (PGE2) and NO.[3,12] Other effects are mast cell degranulation which released mediators that indirectly stimulate afferent nerve endings.[20,21]

In order to recognize the effect of stress to immune response, the study of psychoneuroimmunology should also be understood.[11] Stress consisted of stress perception and stress response. Stress perception is the product of learning process for selecting, organizing, interpreting and implicating the actual stressor. Stress perception reflects cognitive alterations, whereas stress response reflects physiological or biological alterations.[22] Stress, mediated by CNS, activates the hypothalamic-pituitary-adrenal axis (HPA-axis) and increases the cortisol secretion. At the same time, stress also activates the sympathetic-adrenal medullary axis (SAM-axis) to produce more catecholamines (noradrenalin and adrenalin).[11,16]

Peripheral blood monocytes from certain individuals with hyperinflammatory monocytes phenotype secrete are 3–10 folds greater than those with normal monocyte phenotype individuals, and this condition exist in patients with early onset periodontitis or refractory periodontitis. Upon stressful condition, high-stress perception individuals also produce IL-1β, TNF-α and IL-6 that significantly higher compared to low-perception individuals.[23,24]

In this patient who had symptoms mimicking MARD, the stress in his work was suspected as the main trigger of the existing symptoms. Stress impaired body defense reaction to local infection. Altered mood and emotional condition may be involved in the periodontal disease, stress is suggested to affect periodontal health by increasing the level IL-1β, TNF-α and IL-6.[12]

Oral inflammation may propagate to distant targets could be through the interplay of immunogenic and neurogenic inflammation.[20] Interplay between immunogenic and neurogenic inflammation is termed "neurogenic switching."[21] Immunogenic inflammation may initiated by mast cell degranulation which induced by antigens, bacteria,, proteoglycans LPS, neuropeptides (i.e. substance P, SP; CGRP), chemokines, calcium ionophores and physical factors.[25] Degranulated mast cells release histamine and tryptase which may stimulate neurogenic inflammation by binding to a protease activated receptor (PAR) in afferent nerve fibers.[20] The increased level of TNF-α, SP and CGRP was confirmed in a study in Wistar rats injected with *P. gingivalis* LPS (*Pg*LPS).[13]

In chronic gingivitis, histopathologic alteration in gingival tissue facilitated gingival bleeding after innocuous stimuli i.e. tootbrushing, toothpicking. It was caused by 1) vasodilatation and engorgement of the capillaries and their closure to the surface; 2) thinning and ulcerated sulcular epithelium.[15] Therefore, it was logical that SRP elicited bleeding and resulted in instant disappearing of the symptoms since it also decrease mediators concomitantly with the oozed blood. However, compared to the assisted drainage therapy, SRP had a lesser effect to vasodilatation since piezoelectric scaler had water spray for cooling, this condition led to prevent the increase of gingival local temperature. Subgingival massage enhanced the temperature and also more vasodilatation, thus also resulted in more drainage of the mediators.

As a result, it was supposed to be the effect of the assisted drainage therapy to the existing pro-inflammatory mediators (cytokines, PGE2, bradykinin, NO, SP and CGRP) in the periodontal disease which then may immediately cut off the neurogenic switching mechanism.[4,26] It was confirmed that assisted drainage therapy in rats reduced the TNF-α, and SP and CGRP level.[13]

Since the chief complaint of the patient was vertigo, the headache types (i.e. migraine, tension or cluster headache) were not examined. Nevertheless, there are several theories related to the etiopathogenesis of headache, such as the increase of pro-inflammatory cytokines level[18,19,27] and NO.[27] The involvement of the trigeminal nerve (V2) was associated with the sphenopalatine ganglion (SPG)[26,29] and the neurogenic switching mechanism.[29]

Headache symptoms in this case which accompanied by neck pain or spasm suffered by the patient according to several literatures are diagnosed as migraine.[2,30] Activated primary afferent neurons of trigeminal nerve sends impulses via trigeminus nucleus caudalis which acts as sensory relay center. Neck pain may resulted from the excitation of trigeminus nucleus caudalis which may extend to dorsal horn for stimulation of C2, C3 and C4.[2]

Most of the theories of migraine are the arterial concepts which have been focused on the enlargement of intracranial surface-of-the-brain arteries resulting from their exposure to nitric oxide.[19,27] However, the effect of the release of peptides such as CGRP on the *extra cranial and intra-nasal mucosa* by their corresponding trigeminal nerve branches has been largely overlooked and considerably underrated.[24] According to Cady and Schreiber,[29] sinusitis cases often accompanied by migraine and vice versa which related to the "neurogenic switching" mechanism.

Periodontal ligament in the maxilla is also innervated by V2. Stimulated C fibers from maxillary periodontal ligaments (V2) may antidromically release SP and CGRP,

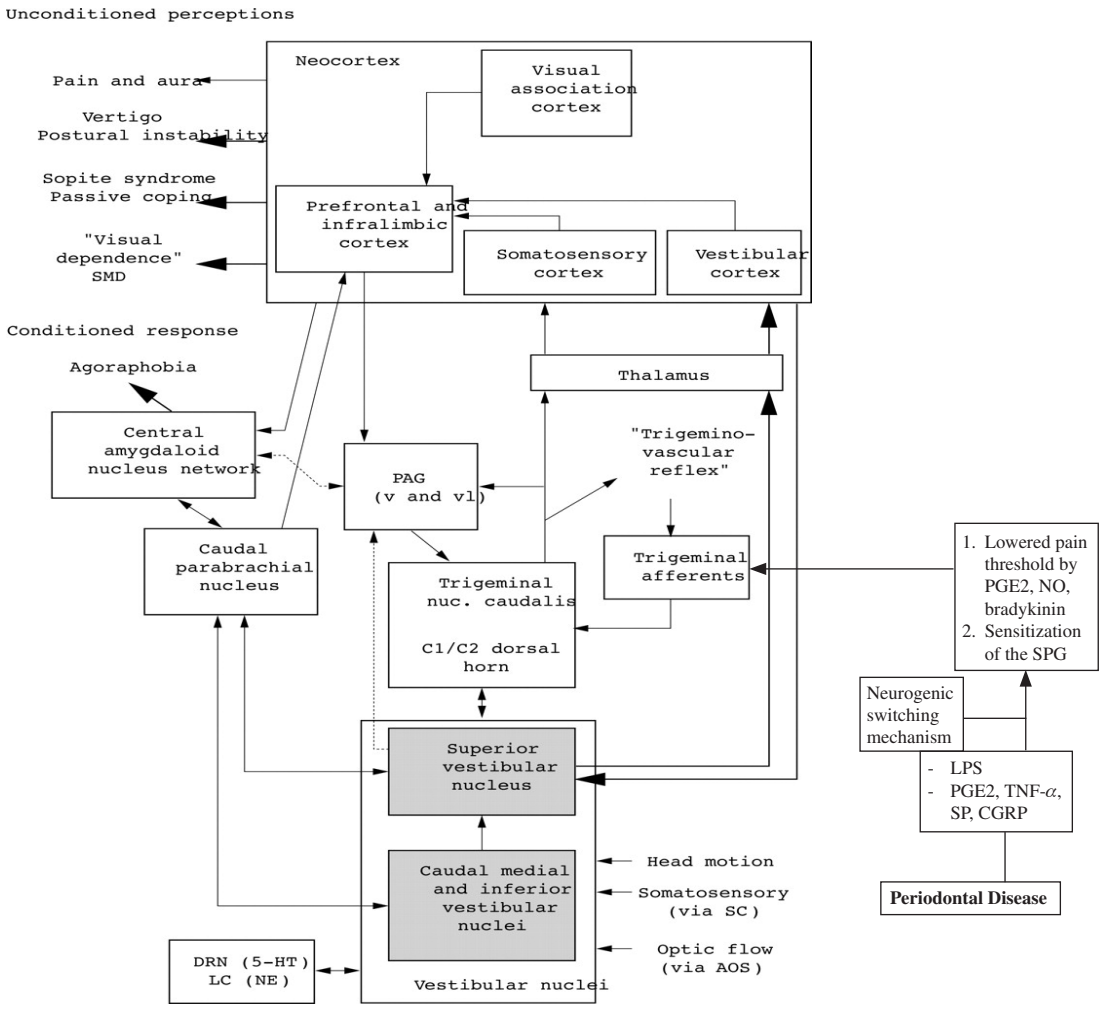

Figure 6. Pathogenesis model for migraine–anxiety related dizziness (MARD) and the relationship with periodontal disease (source; Furman *et al*., 2005).

this mechanism is proposed to be the etiology of sinusitis and migraine.[24,28] Therefore, through the neurogenic switching mechanism, periodontal inflammation may also directly affects sinus inflammation (mucosa and artery) through the neuropeptides release of SP and CGRP by afferent nerve of nasal mucosa via the sphenopalatine ganglion.[20,26,29]

The trigeminovascular reflex, which is related to intracranial arterial vasodilatation due to increase NO concentration or inflammation is a normal mechanism. Neurons of the first division of trigeminal nerve (V1) reported this condition to the trigeminal sensory nucleus. However, in certain individuals with elevated sympathetic tone or pre-sensitized afferent nerves may trigger headache.[26]

According to Furman *et al.*,[1] there is connection between migraine, vertigo and anxiety. Vestibular pathways can contribute to both central and peripheral migraine mechanisms. The reciprocal connections between vestibular nuclei and trigeminal nucleus caudalis suggest that vestibular and trigeminal information processing may be altered concurrently during migraine attacks, and that vestibular signals may directly influence trigeminovascular reflex pathways (Fig. 6).

In addition, central vestibular activation can affect activity in monoaminergic pathways through direct connections from the vestibular nuclei to the dorsal raphe nucleus, nucleus raphe magnus, locus coeruleus, and lateral tegmental region. These changes in monoaminergic activity due to vestibular activation may both trigger migraine related symptoms and modulate activity in both pain related and anxiety related pathways. Conversely, regionally specialized noradrenergic and serotonergic inputs are potential substrates for altering central vestibular information processing during and between migrainous episodes. In addition, anxiety or hyperventilation may also reactivate a vestibular disorder by interfering with central compensation or by altering somatosensory input.[1]

There are three way interfaces among migraine, anxiety, and dizziness. The interactions between the balance–migraine and the balance–anxiety interfaces are shown schematically on the upper left. Neuronal activity in the vestibular nuclei, particularly the superior vestibular nucleus, is a first major integrative site for the

balance–migraine–anxiety linkage. As this activity is a function of a) afferent input regarding head motion from the inner ear, somatosensation from the spinal cord (SC) and optic flow information from the accessory optic system (AOS); b) trigeminal sensory inputs; and c) descending inputs from the neocortex, it has the potential to participate in the triggering, buildup, and perseverance of episodic dysfunction.[1] The role of periodontal disease in neurogenic switching mechanism is shown on the lower right.

Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); AOS, accessory optic system; DRN, dorsal raphe nucleus; LC, locus ceruleus; NE, norepinephrine; PAG (v and vl), periaqueductal grey (ventral and ventrolateral columns); SC, superior colliculus; SMD, space and motion discomfort.

Periodontal disease is the source of LPS, pro-inflammatory mediators including PGE2, NO and bradykinin[3,12] that were able to lower pain threshold of the afferent nerve fibers of the trigeminal nerve[31] (Fig.5). It was also proposed to be involved in the sensitization of the sphenopalatine ganglion (SPG) which related to migraine.[4,26]

Vertigo in this patient may also caused by the release of SP from local sensory nerve fibers in the inner ear that stimulates expression of endothelium–leukocyte adhesion molecules from cochlear microvasculature. This mechanism decreases blood flow to cochlear sites resulting vestibular disorders.[18] In animal study it was verified that *Pg*LPS injection increase SP in nasal tissues which closely related to the vestibular system and the assisted drainage therapy also decrease SP level in nasal tissues.[13]

The instant relief of headache, improve of eyesight and other symptoms after scaling procedures may be caused by decreasing of the neurogenic switching mechanism. The oozed blood during scaling should contain pro-inflammatory mediators, bacteria and LPS which may directly cut off the neurogenic switching mechanism.[4] This phenomenon was verified by the decrease of TNF-α, SP and CGRP levels several minutes after the assisted drainage therapy in rat model.[13]

This case report is a retrospective study of patient suffered from symptoms mimicking MARD according to the patient's medical history and examined by a dental practitioner. Further studies with the true MARD should be done in collaboration with competent medical practitioners and comprehensive medical diagnostic procedures

Conclusion: Based on the remarkable result of the periodontal treatments and supported by animal study related to this evidence-base case report, it is concluded that: 1) correlation oral focal infection, especially periodontal disease with illnesses mimicking MARD symptoms should be exist; 2) Periodontal treatments such as SRP and the assisted drainage therapy are beneficial in MARD management. Nevertheless, further investigation should be done about the etiopathogenesis of periodontal – systemic related illnesses and increase the multidisciplinary approach in the scope of dentistry and general medicine to explore new interrelated cases.

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