NEW PARADIGM IN ORAL FOCAL INFECTION:
PERIODONTAL DISEASE AS AN ETIOLOGY OF MIGRAINE-ANXIETY RELATED DIZZINESS (MARD)

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ABSTRACT

Recently, two CNS disorders, migraine and anxiety, have been recognized as being commonly associated with dizziness. These associations may be an expression of an aetiological relationship, for example, dizziness caused by migraine, or dizziness caused by anxiety; alternatively, migraine or anxiety may influence the presentation of a balance disorder. For example, chronic dizziness may become more disabling during the added stress of a migraine headache or panic attack. In addition, dizziness occurs comorbidly with both migraine headache and anxiety disorders. Finally, there is increased comorbidity between anxiety and migraine. Thus, it is not surprising that some patients with dizziness may suffer from a combination of a balance disorder, migraine, and an anxiety disorder, a symptom complex was proposed to name migraine–anxiety related dizziness (MARD). There had been increasing numbers of literatures and evidence-based cases linking periodontal disease to several systemic diseases. Various mechanisms were proposed to explain the etiopathogenesis by which periodontal disease caused systemic diseases. However, systemic effects of periodontal disease that lead to several symptoms such as migraine, dizziness (vertigo) and other debilitating complaints are rarely discussed. The objective of this study is to propose the mechanism of periodontal disease involvement in the etiopathogenesis of MARD. Periodontal treatment which done to a patient suffered from symptoms mimicking MARD resulted in instant disappearing of most of the symptoms. Regarding to remarkable result, the conclusion is that periodontal disease could be a source of neurogenic and immunogenic inflammation which if not treated periodically could perpetuate symptoms mimicking MARD.

Keywords: oral focal infection, migraine-anxiety related dizziness

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INTRODUCTION

Migraine-anxiety related dizziness (MARD), is a new term proposed by Furman et al. 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 (Furman et al., 2005). 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 (Furman et al. 2005). The possible link between oral focal infection and non-oral diseases had been studied by Li et al. based on the evidence-based case reports (Li et al. 2000). In addition, several case reports revealed that elimination of oral focal infection had beneficial effects to sinusitis (Utomo 2006) and headache (Utomo & Prahasanti 2005; Utomo 2006) and symptoms mimicking Chronic Fatigue Syndrome (CFS) (Utomo 2005). However, studies related to the link between periodontal disease and the etiopathogenesis of MARD is still uncommon.

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 neuro-psychological complaints which lasting more than 6 months and coupled with 6 or more arbitrary symptoms (Victor & Ropper 2001; Strauss 2005). 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. Something particular in CFS patient is lower than normal blood cortisol level (Craig & Kakumanu 2002; Strauss 2005). 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 (Padgett & Glaser 2003). 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. Periodontal treatment that had been conducted to a patient suffered from symptoms mimicking MARD was able to relief all of the symptoms.

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.

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 tredmills, 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 gastritis and duodenal ulcer), chlor Diazepoxide + clindium (anti-anxiety), clobazam and alprazolam (tranquilizer), bisoprolol fumarate (anti hypertensive, angina pectoris) and acetyl salicylic acid (as an anticoagulant).

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. Probing revealed that deep periodontal pockets existed in every region, especially over the left posterior teeth. No caries was found. Periodontal treatment in several literatures was able to reduce or eliminate several symptoms such as headache, sinusitis, fatigue, muscle pain or spasms (Utomo 2005; Utomo & Prahasanti 2005; Utomo 2006). 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. One year later and the next six months which was in May 2006, the patient was evaluated, and the symptoms did not reappear.

The purpose of this study is to reveal the possibility of the oral focal infection involvement in the etiopathogenesis of MARD, based on the remarkable result of periodontal treatment 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.

**DISCUSSION**

Researches done by Li et al. revealed the possibility of the relationship between oral focal infection and non-oral diseases. Metastatic spread of infection from oral cavity which may be done in several ways were shown in Table 1 (Li et al, 2000).

Table 1. Possible pathways of oral infections

<table>
<thead>
<tr>
<th>Pathway for oral infection</th>
<th>Possible non-oral disease</th>
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<tbody>
<tr>
<td>Metastatic infection from oral cavity via transient bacteremia</td>
<td>Subacute infective endocarditis, acute bacterial myocarditis, brain abscess, cavernous sinus thrombosis, sinusitis, lung abscess/infection, Ludwig’s angina, orbital cellulitis, skin ulcer, osteomyelitis, prosthetic joint infection</td>
</tr>
<tr>
<td>Metastatic injury from circulation of oral microbial toxins</td>
<td>Cerebral infarction, acute myocardial infarction, abnormal pregnancy outcome, persistent pyrexia, idiopathic trigeminal neuralgia, toxic shock syndrome, systemic granulocytic cell defects, chronic meningitis</td>
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<tr>
<td>Metastatic inflammation caused by immunological injury from oral organisms</td>
<td>Behcet’s syndrome, chronic urticaria, uveitis, inflammatory bowel disease, Crohn’s disease</td>
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(Adapted from Li et al., 2000)

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 proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) that may also affected the brain if produced in sufficient concentration (Licinio & Frost 2000; Kiecolt-Glaser & Glaser 2002).

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 (Dantzer 2001; Kiecolt-Glaser & Glaser 2002) and nitric oxide.
Lipopolysaccharide challenge upregulates the expression of endothelial cells adhesion molecules-1 and stimulate the release of high levels of inflammatory mediators by macrophages or monocytes and stimulate the release of high levels pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, prostaglandin E2 (PGE2) (Li et al. 2000; Madianos et al. 2005) and NO (Madianos 2005). Other effects are mast cell degranulation (Supajatura 2002) and indirectly stimulate afferent nerve endings (Lundy & Linden 2004).

Peripheral blood monocytes from certain individuals with hyperinflammatory monocyte phenotype secrete 3–10 folds greater than those with normal monocyte phenotype individuals, and this condition exist in patients with early onset periodontitis or refractory periodontitis (Shapira et al. 2005). Upon stressful condition, high-stress perception individuals also produce IL-1β, TNF-α and IL-6 that significantly higher compared to low-perception individuals (Kamma et al. 2004). Pro-inflammatory cytokines are also capable of stimulating glucorticoid synthesis through the HPA axis (Licinio & Frost 2000; Padgett & Glaser 2003; Roitt & Delves 2001). Interleukin-6, which is also elevated by stress and adrenaline (Kamma 2004), is a potential stimulator of HPA axis resulting in cortisol secretion to help control the inflammation (Licinio & Frost 2000). Unfortunately, high cortisol level depresses immune function (Padgett & Glaser 2003).

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 (Kamma et al. 2004). As a consequence of unsuccessful elimination of oral focal infection, in this case periodontal infection, may perpetuate the systemic infection and the cytokine induced-sickness behavior did not come to an end. These never ending sickness behavior may be related to the debilitating symptoms (Licinio & Frost, 2000).

Oral inflammation may propagate to distant targets could be through the interplay of immunogenic and neurogenic inflammation (Lundy & Linden 2004). Interplay between immunogenic and neurogenic inflammation is termed “neurogenic switching” (Boyd 2005; Meggs 1997). Immunogenic inflammation may initiated by mast cell degranulation which induced by antigens, bacteria, proteoglycans LPS, neuropeptides (i.e. substance P, SP), chemokines, calcium ionophores and physical factors (Walsh 2003). Degranulated mast cells release histamine and tryptase which may stimulate neurogenic inflammation by binding to a protease activated receptor (PAR) in afferent nerve fibers (Lundy and Linden, 2004). Additionally, pro-inflammatory cytokines and NO released by LPS-induced macrophage or monocytes, and bradykinin from damaged tissue are able to stimulate neuropeptides release from local afferent sensory fibers in the periodontal tissue. Stimulated nerve fibers release neuropeptides i.e. SP, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptides (VIP) and neuropeptide Y (NPY) (Lundy and Linden, 2004). There was a plausible explanation regarding to the instant disappearing of the symptoms which related to the oozed blood that occurred during the periodontal treatment. It was supposed to be an assisted drainage to the existing pro-inflammatory mediators (cytokines, PGE2, bradykinin, NO) in the periodontal disease which then may immediately “cut off” the neurogenic switching mechanism (Utomo 2006). 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 (Dantzer 2001; Jeong et al. 2003; Stirparo et al. 2000), NO (Stirparo 2000), involvement of the trigeminal nerve (V2) associated with the...
signals may directly influence trigeminovascular reflex (Furman et al. 2005). Headache symptoms in this case which accompanied by neck pain or spasm suffered by the patient according to several literatures are diagnosed as migraine (Green 2005; Unger et al. 2005). Activated primary afferent neurons of trigeminal nerve sends impulses via trigeminus nucleus caudalis which acts as sensory relay center. Neck pain may result from the excitation of trigeminus nucleus caudalis, which may extend to dorsal horn for stimulation of C2, C3 and C4 (Green 2005).

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 (Boyd 2005; Stirparo 2000). 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 (Boyd 2005). According to Cady and Schreiber, sinusitis cases often accompanied by migraine and vice versa which related to the “neurogenic switching” mechanism (Cady and Schreiber 2002). Periodontal ligament in the maxilla is also innervated by V2. Stimulated C fibers from maxillary periodontal ligaments (V2) may antidromically release SP and CGRP, this mechanism is proposed to be the etiology of sinusitis and migraine (Boyd 2005; Okeson 2005). Therefore, through the neurogenic switching mechanism (Lundy and Linden, 2004), 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 (Boyd 2005).

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 (Boyd 2005). According to Furman et al, 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 (Figure 1) (Furman et al 2005). 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 (Figure 1) (Furman et al. 2005).

Periodontal disease is the source of LPS, pro-inflammatory mediators (Li et al. 2000) including PGE2, NO and bradykinin (Madianos, 2005) that were able to lower pain threshold of the afferent nerve fibers of the trigeminal nerve (Kidd & Urban 2001) (Figure 1). It was also proposed to be involved in the sensitization of the sphenopalatine ganglion (SPG), which related to migraine (Boyd 2005; Klinghardt 2005; Utomo 2006). 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 microvasculatures. This mechanism decreases blood flow to cochlear sites resulting vestibular disorders (Stirparo et al. 2000).

Other possibility is the release of Gingipains R, a proteolytic enzyme from P gingivalis which triggers decreased of blood flow, especially in microvasculatures. Gingipains R in the bloodstream can activate factor IX, factor X, prothrombin, and C reactive protein, thus promoting a thrombotic tendency through the release of thrombin, subsequent platelet aggregation, conversion of fibrinogen to fibrin and intravascular clot formation (Li et al., 2000). Visual disturbances such as blurred vision and symptoms mimicking intermediate or posterior uveitis (White & de Paolis 2005), may be induced by proinflammatory cytokines or LPS originated from the periodontal infection via the blood stream (Li et al. 2000). Another possibility is by the neurogenic switching mechanism related to afferent nerves of V1 (ophthalmic division of trigeminal nerve) (Herndon 2006; Yang et al. 1998). Palpitations may be caused by noradrenaline or adrenaline, released in the state of stress to stimulate the body defense system, especially increase of heart rate and force heart contraction (Sherwood 2005). Patient might already have phobia to certain circumstances, which could exacerbate the vertigo, such as looking down through the airplane window.
Figure 1. Pathogenetic model for migraine–anxiety related dizziness (MARD) and the relationship with periodontal disease (adapted from Furman et al., 2005). There are three-way interface 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 perseverence of episodic dysfunction. The role of periodontal disease in neurogenic switching mechanism is shown on the lower right. 

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 (Utomo, 2006). Gradual remission of pain and spasm in muscles should be caused from the diminish of hyperalgesia and sensitization of afferent nerve fibers which formerly caused by high concentration of PGE2, bradykinin and NO.

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. Based on the remarkable result of the periodontal treatment and supported by literature
reviews in case reported, it is concluded that a correlation oral focal infection, especially periodontal disease with illnesses mimicking MARD symptoms should be exist. 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.

REFERENCES


