THE UVEITIS – PERIODONTAL DISEASE CONNECTION IN PREGNANCY: CONTROVERSY BETWEEN MYTH AND REALITY

Widyawati Sutedjo1, Chiquita Prahasanthi1, Daniel Haryono Utomo2
1 Department of Periodontology, Airlangga University
2 Dental Clinic Faculty of Dentistry, Airlangga University

ABSTRACT

Background: Recently, it had been recognized that oral infection, especially periodontal disease are potential contributing factors to a variety of systemic diseases, such as cardiovascular and cerebrovascular diseases, pregnancy problem, diabetes mellitus type 2, etc. However, the adverse effect of periodontal disease toward uveitis still not clearly understood especially if happens during pregnancy. Interestingly, in Indonesia, there is still a myth that pregnant women should not get any dental treatment, therefore, it may deteriorate periodontal disease during pregnancy. Purpose: to explain the possible connection between periodontal disease and uveitis and increase the awareness of these problems during pregnancy that could be understood by doctor and laymen. Reviews: literatures revealed that dental infection can caused uveitis via metastatic spread of toxin and inflammatory mediators. Additionally, more recent investigation reported that the neural system may also stimulated by oral infection. In the orofacial regions there’s trigeminal nerve complex that also related to the orbital region, thus may also involved in the uveitis pathogenesis. The effects of periodontal pathogens toxins toward immunocompetent cell and nerves had also been reported by researcher. Moreover, pregnant women are more susceptible to periodontal disease, therefore maintaining oral hygiene and dental monitoring is a mandatory. Conclusion: in woman who susceptible to uveitis, periodontal disease may exacerbate the symptoms especially in pregnancy. Therefore simple explanation about connection of oral infection-systemic diseases especially in pregnancy should be widespread among Indonesian people.

Key words: periodontal disease, uveitis connection, Indonesian, myth

INTRODUCTION

In recent years there has been a reawakening of the dangers of oral infections and their potential disastrous effects on systemic health. Gingivitis and periodontitis is the potential sources of this oral infection. In modern dentistry by performing a treatment called scalling root planning, curretage or Assisted Drainage Treatment (ADT) must surely be one of the prime candidates for this reassessment. As dentists we are indoctrinated that it is better to keep the oral hygiene to prevent from any other diseases by teaching how to keep the oral hygiene.

Historically, periodontal disease was regarded as an infection caused by bacterial species that colonize the periodontal pocket. Microbial products trigger the release of proinflammatory cytokines and host derived enzymes, the excessive and/or dysregulated production may results in tissue breakdown. The impact of microbial products such as lipopolysaccharide (LPS) on induction of immune responses, toll like receptor (TLR) signaling and cytokine networks is crucial to inflammatory changes that develop in the tissues. Elevated levels of tissue-destructive enzymes such as matrix metalloproteinase’s (MMPs) and proinflammatory cytokines can be detected in the gingival crevicular fluid (GCF) and saliva of patients with periodontitis. The pathogenic inflammatory mechanisms may lead to the development and progression of disease.

A possible correlation of focal infection with uveitis could be predicted regarding to an object observation of a phenomenon that related to the uveitis symptoms.
Periodontal treatment that had been conducted to a patient suffered from symptoms uveitis was able to relief all of the symptoms.

A 30 year old female patient come to the clinic. She is a housewife and suffered from several symptoms such as headache, neck pain and spasm, eye redness; blurring of vision; watery; pain and sensitivity to light. The illnesses started 1 year earlier and the treatment and medications had already been conducted by general practitioner and ophthalmologist. Her doctor said that she got the uveitis.

There were a lot of prescribed drugs such as, Medison (corticosteroid) and Sandimun (corticosteroid). But she is not getting better and she come to the dentist. From physical examination, despite her moonface (because of the usage of corticosteroid long term), 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 (5 mm) existed in left and right posterior teeth maxilla and right posterior teeth mandible especially over M1 and M2. No caries was found.

Periodontal treatment in several literatures were able to reduce or eliminate several symptoms such as headache, sinusitis, fatigue, muscle pain or spasms. The same result also occurred in this patient, who had no more headache, redness of the eye, blurring of vision and everything were normal again.

The purpose of this article review is to reveal the possibility of the periodontal disease involvement in the etiopathogenesis of Uveitis, based on the remarkable result of periodontal treatment to a patient suffered from uveitis. However, further researches should be done to support the validity of this successful clinical evidence-based case treatment.

LITERATURE REVIEWS

What is uveitis? Uveitis is an inflammation of the uveal tract, The middle layer between the sclera and the retina is called the uvea. The uvea contains many of the blood vessels which nourish the eye. Inflammation of the uvea can affect the cornea, the retina, the sclera, and other vital parts of the eye. Uveitis can also be related to diseases in other parts of the body, such as arthritis or may be caused by infectious agents (e.g., Pneumocystis carinii), may be idiopathic (e.g., sarcoidosis), or may be autoimmune in origin (sympathetic ophthalmia).5

The Symptoms of Uveitis include light sensitivity, blurring of vision, pain, redness of the eye and headache.5 Nevertheless, there are several theories related to the etiopathogenesis of headache, such as the increase of pro-inflammatory cytokines level,6,7,8 NO6 involvement of the trigeminal nerve (V2) associated with the sphenopalatine ganglion (SPG)9,10 and the "neurogenic switching" mechanism.11

Systemic Effects of Periodontal Disease. In abundant literatures reported the effect of periodontal diseases to systemic diseases such as cerebrovascular, cardiovascular diseases, diabetes mellitus type 2, etc. Several researchers also revealed the effect of periodontopathic bacteria part i.e. lipopolysaccharides, fimbriae, whole bacteria to systemic condition including allergy. According to a research by Utomo in 2009, by injection LPS1435/1450 Porphyromonas gingivalis (Pg LPS1435/1450) with low dosage on a gingival sulcus maxillawistar rat. On the 14th day, had found the increases of mRNA SP and CGRP in the bronkus.12 Moreover on the research by Abd El-Aleem et al., 2004 who injected Salmonella typhimurium intragingival on the papil interdental between first and second molars of wistar rat mandible. On examination with the hybridization in situ on days 3, 7 and 10 and found an increase level of SP and CGRP mRNA in various branches of the n. Trigeminal, namely n. Mandible, n. Maxilla and n. Ophthalmicus. The study of LPS used and injected in the upper jaw Pg LPS1435/145013 And it is possible that periodontal disease can cause uveitis.

Host immune response and periodontal disease is a common, complex, inflammatory disease characterized by the destruction of tooth-supporting soft and hard tissues of the periodontium, including alveolar bone and periodontal ligament (PDL). Although the inflammation is initiated by bacteria, the tissue breakdown events that lead to the clinical signs of disease result from the host inflammatory response that develops to combat the challenge presented by the subgingival biofilm.1

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).14

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) 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 cytokines7,17 and nitric oxide (NO) which is produced by inflammation and infection.6 In addition, CFS is closely related with cytokine-induced sickness behavior.16,17

There is a possibility that Uveitis also related to cytokine-induced behavior. Bacterial endotoxins (lipopolysaccharides, LPS) are part of outer cell wall of Gram-negative bacteria. Lipopolysaccharide challenge upregulates the expression of endothelial cells adhesion
In order to recognize the effect of stress to immune response, the study of psychoneuroimmunology should also be understood. Stress consisted of stress perception and stress response. Stress, mediated by CNS, activates the hypothalamic-pituitary-adrenal axis (HPA-axis) and increases the cortisol secretion. At the same time, the hypothalamic-pituitary-adrenal axis (HPA-axis) and stress response, the study of psychoneuroimmunology should also be understood.

In this patient who had Uveitis, 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 that significantly higher compared to low-perception individuals also produce IL-1β, TNF-α, and IL-6.

Pro-inflammatory cytokines are also capable of stimulating glucocorticoid synthesis through the HPA axis. Interleukin-6 which is also elevated by stress and adrenaline is a potential stimulator of HPA axis resulting in cortisol secretion to help control the inflammation. Pro-inflammatory cytokines and NO released by LPS-induced macrophage or monocytes, and bradykinin from damaged tissue are able to stimulate pro-inflammatory mediators release from local afferent sensory fibers. Degranulated mast cells release histamine and tryptase which may stimulate neurogenic inflammation by binding to a protease activated receptor (PAR) in afferent nerve fibers.

Additionally, pro-inflammatory cytokines and NO released by LPS-induced macrophage or monocytes, and bradykinin from damaged tissue are able to stimulate pro-inflammatory mediators release from local afferent sensory fibers. Degranulated mast cells release histamine and tryptase which may stimulate neurogenic inflammation by binding to a protease activated receptor (PAR) in afferent nerve fibers.

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 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.

Oral inflammation may propagate to distant targets could be through the interplay of immunogenic and neurogenic inflammation. Interplay between immunogenic and neurogenic inflammation is termed "neurogenic switching".

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. Degranulated mast cells release histamine and tryptase which may stimulate neurogenic inflammation by binding to a protease activated receptor (PAR) in afferent nerve fibers.

| Pathway for oral infection | Possible nonoral disease |
|---------------------------|-------------------------|
| Metastatic infection from oral cavity via transient bacteremia | Subacute infective endocarditis, acute bacterial myocarditis, brain abscess, cavernous sinus thrombosis, sinusitis, lung abscess/infection, Ludwig's angina, orbital cellulitis, skin ulcer, osteomyelitis, prostatic joint infection |
| Metastatic injury from circulation of oral microbial toxins | Cerebral infarction, acute myocardial infarction, abnormal pregnancy outcome, persistent pyrexia, idiopathic trigeminal neuralgia, toxic shock syndrome, systemic granulocytic cell defect, chronic meningitis |
| Metastatic inflammation caused by immunological injury from oral organism | Behcet's syndrome, chronic urticaria, uvetitis, inflammatory bowel disease, Crohn's disease |

(Adapted from Li et al., 2000)
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.9

CONCLUSIONS

Periodontal disease is the source of LPS, proinflammatory mediators14 including PGE2, NO and bradykinin18 that were able to lower pain threshold of the afferent nerve fibers of the trigeminal nerve30 (figure 1). 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 active 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.14 Visual disturbances such as blurred vision and posterior uveitis,14 may be induced by proinflammatory cytokines or LPS originated from the periodontal infection via the blood stream.14 Another possibility is by neurogenic switching mechanism related to afferent nerves of V1 (ophthalmic division of trigeminal nerve).33,34 Palpitation 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.35

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

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 review article base on an evidence based case of patient suffered from uveitis according to the patient's medical history and examined by a dental practitioner. Further studies with the true uveitis 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 uveitis 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.

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