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IS THERE ANY LINK BETWEEN CHRONIC PERIODONTITIS AND MIGRAINE? A NARRATIVE REVIEW.

Dentistry

Dr. Alina Pauly* Senior lecturer, Department of Periodontology, Rajarajeswari Dental College and Hospital, Bangalore, India. *Corresponding Author

Dr Sharika Gopinath Senior lecturer, Department of Periodontology, Rajarajeswari Dental College and Hospital, Bangalore, India.

Dr Ann Shaji Postgraduate, Department of Periodontology, Rajarajeswari Dental College and Hospital, Bangalore, India.

ABSTRACT

Chronic periodontitis is an infectious inflammatory disease affecting the periodontium which is caused by bacterial products evoking an immune response which could result in the destruction of the periodontium and ultimately leads to tooth loss. Around 1 billion individuals worldwide suffer from migraines, a neurologic condition that causes excruciating throbbing pain on one side of the brain. This narrative review highlights the association between chronic periodontitis and migraine, as many studies reveals that they share common inflammatory mediators and biomarkers which ultimately lead to the progression of the diseases. However, more evidence is necessary to investigate if chronic periodontitis could be considered as a risk indicator of chronic migraine.

KEYWORDS

INTRODUCTION

Chronic gingival infection known as periodontitis is characterized by bone loss and destruction of the periodontal tissue. [1] Based on the 2016 Global Burden of Disease Study, severe periodontitis was the 11th most prevalent condition in the world.[2]The occurrence of periodontal disease was reported to range from 20% to 50% around the world. [3]Recently, it has been proposed that periodontitis not only produces local effects in the gingiva but also has the potential to have systemic effects. It is suggested that subgingival pocket epithelium creates a simple communication for the periodontopathogens to enter the bloodstream. Additionally, lipopolysaccharides and other bacterial components may be circulated in the blood. Together with bacterial antigens, these endotoxins have the potential to cause significant systemic inflammatory reactions including in other distant organ systems like the brain.[4]

The primary chronic headache condition known as migraine is characterized by repeated attacks of severe, incapacitating headaches that are typically unilateral, pulsatile and accompanied by other symptoms like nausea or vomiting as well as increased sensitivity to light and noise. This condition affects more than 11% of the general population and affects women more frequently (18%) than men (6%). Due to the fact that 80% of migraine patients experience some level of disability as a result of their headaches, the World Health Organization has listed this condition as one of the most debilitating diseases. Episodic migraine (EM) and chronic migraine (CM) are the two primary kinds of migraine. The primary issue with EM is its chronic nature, which has a 3% annual rate of progression and in the pathophysiology of migraine, activation of the trigeminovascular system and cortical spreading depression have both been suggested. Some of the risk factors for migraine progression include excessive use of acute migraine medications, ineffective acute therapy, obesity, depression, low educational status, and stressful life events.[5] This review focuses on the relationship between chronic periodontitis and migraine.

Pathophysiology Of Migraine And Periodontitis

The proposed link between periodontitis and migraine may be explained by a number of pathophysiological mechanisms, including systemic and neurogenic inflammation, endothelial dysfunction, and matrix protease dysfunction. Additionally, these diseases share a number of systemic problems, including insulin resistance, hypertension, hypercholesterolemia, and vascular atherosclerotic disorders. Disability levels rise as a result of migraine chronification, and treatment effectiveness rates drop. Identification of modified risk factors like depression, obesity, low socio economic status and income is recommended. Apart from this, studies suggest that periodontitis act as a major factor for the progression of migraine chronicity due to the shared inflammatory mediators and biomarkers. This is an accurate suggestion as gingival tissues' inflammatory response to periodontal disease produces numerous inflammatory mediators that might be a factor in migraine development attacks, therefore promoting the chronification of migraine. It appears likely that periodontal disease is caused as a result of interaction between host, microbes, cytokines and acute-phase reactants (IL-1, TNF-a, CRP, and IL-6) that are produced. Endotoxemia is the cause of the systemic and local spread possibly from a persistent low-grade inflammatory condition resulting in an overexpression of neurogenic biomarkers, including CGRP, SP, and NKA while a chronic migraineur is in the interictal phase. The proposed mechanism between migraine and chronic periodontitis is explained in fig 1. [6]

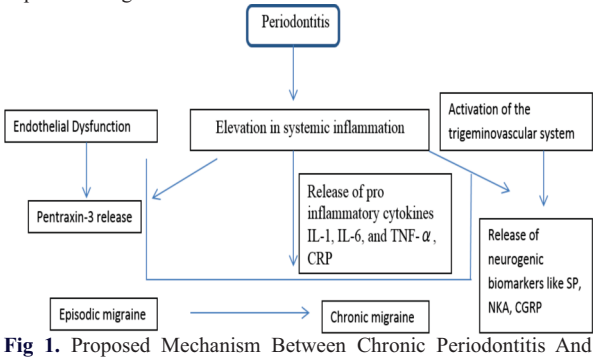


Fig 1. Proposed Mechanism Between Chronic Periodontitis And Migraine

Common Factors Associated With Periodontal Disease And Migraine

1. *Inflammatory markers*

Studies have shown that pro inflammatory markers like C-reactive proteins, IL-1, IL-6, and TNF – α elevated in periodontitis are also observed in the blood streams of migraine sufferers leading to vascular dysfunction.

2. *Changes in endothelial function*

The three most common findings in periodontitis and migraine patients are:

- Increased levels of fibrinogen in the blood
- Reduction in endothelial progenitor cells
- Rise in pentraxin-3 level

Increase in fibrinogen results in smooth muscle damage causing smooth muscle proliferation and migration. Research showed elevated levels of fibrinogen and von Willebrand factor in migraine patients suggestive of systemic inflammation. Similar findings were observed in periodontitis patients also. Endothelial progenitor cells helps in the repair and regeneration of damaged vessels. These cells are reduced in migraine patients, resulting in a reduction in migratory capacity and

cellular damage. Periodontitis patients have elevated levels of circulating endothelial progenitor cells.

Another important factor common for the endothelial damage is the increased levels of Pentraxin – 3. Pentraxin -3 is an acute phase protein which is produced at the site of inflammation by PMN's, macrophages, endothelial cells and dendritic cells. It alters inflammatory cells and stimulates vascular inflammation. By reducing the nitric oxide (NO) production, pentraxin-3 inhibits cell proliferation and alters their function from within the endothelial cells. Similarly levels of Pentraxin -3 are elevated in the GCF and plasma of periodontitis patients.[6]

Dysfunction Of Matrix Protease

Biomarkers connected to vascular repair/remodelling, such as matrix metalloproteinase-9 (MMP9) has also been linked to migraine. MMPs are thought to be crucial in periodontal deterioration.[8] Additionally; migraineurs have plasma levels of MMP-9 that are noticeably higher than those of control patients.[9]

Immune Response Alterations

Immune-mediated pathways in the vascular endothelium are involved in the pathophysiology of migraine. The master regulators of innate immune function known as toll-like receptors (TLRs) have a role in the stimulation of inflammatory responses in the brain as both the innate immune system of the host and the activation of adaptive immunity have been linked to TLRs.[6]

Increase Of Mediators Of Neurogenic Inflammation

It has been proposed that periodontal disease (PD) could act as a systemic inflammatory vascular stressor that contributes to the process of migraine chronification. In addition, levels of sensory neuropeptides that were thought to be involved in pathophysiology of migraine such as neurokinin A (NKA) and substance P are increased in both the gingival crevicular fluid and plasma of PD patients. It has been hypothesized that inflammation within the periodontal tissues is associated with the release of several pro-inflammatory molecules that could be involved in the onset of migraine attacks therefore facilitating migraine chronification. It could be speculated that vasodilation produced by periodontal inflammation might elevate the net rate of CGRP removal from the gums and increase circulating CGRP levels, thus, promoting migraine chronification.[1] In addition, both diseases share several systemic conditions including hypercholesterolemia, hypertension, insulin resistance, and vascular atherosclerotic diseases. Further, chronic low-grade inflammation releases a large number of inflammatory mediators and biomarkers, which could account for the overexpression of these biomarkers (CGRP, substance P and NKA). Periodontal infection may further stimulate the trigeminovascular system, which comprises tiny pseudo unipolar sensory neurons originating from the trigeminal ganglion and upper cervical dorsal nerve root, both of which are involved in the chronification of migraine.[10]

Other Systemic Conditions Associated With Migraine And Periodontal Disease

Studies have found the prevalence of certain other systemic conditions together with migraine and chronic periodontitis.

Coronary Heart Disease

Periodontal pathogens enter in to the blood stream and activate the host immune responses. As a result, atherosclerotic plaque formations are seen in the arteries. Positive correlation has been found between PD, migraine and risk of coronary heart disease with a female predilection for migraine and coronary heart disease. Periodontal therapy can reduce the level of c-reactive proteins and thus improve the clinical parameters[6].

Cerebrovascular Disease

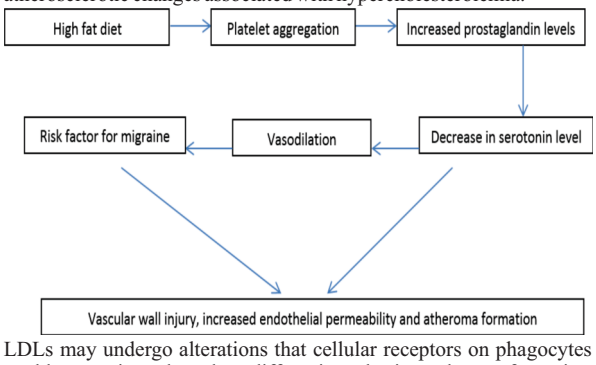
An association between migraine and ischemic strokes has been established, with an increased risk in women in their fourth decade of life. A recent metaanalysis have found that, patients with repeated attacks of migraine tend to have increased chance of developing both PD and CVD[6].

Hypertension

Patients with chronic migraine are more susceptible for developing hypertension than EM. Other types of migraines and headaches associated with auras have a significant association with hypertension. Similiarly, periodontitis patients also show an increased chance of developing hypertension. The mechanisms behind both are associated with the dissemination of bacterial pathogens in the blood streams, and increase in the systemic inflammation.[11]

Hypercholesterolemia

Patients with migraine have increased levels of LDL, risking atherosclerotic changes associated with hypercholesterolemia.[6]



LDLs may undergo alterations that cellular receptors on phagocytes could recognize when they diffuse into the inner layer of arteries. Lipids may cause the sub endothelial macrophages to become dilated, which causes them to develop into foam cells in the early stages of atheroma development. [12] The production of inflammatory mediators from activated macrophages may stimulate endothelial cells, which in turn may release chemotactic cytokines and activate the receptors necessary for the recruitment of monocytes to atherosclerotic lesions. Regarding PD, the systemic spread of the bacterium and the presence of lipopolysaccharides (LPS) in the plasma may boost the hepatic production of cholesterol, which may be delivered as lipids that will bind to bacterial LPS. This provides an explanation for how dyslipidemia, atherogenesis, and periodontal infection interact.[12]

According to clinical investigations, people with PD have greater total serum cholesterol levels than people who are healthy .[13,14]

Insulin Resistance

Periodontal disease has a bidirectional relationship with diabetes. Studies suggest that, periodontal treatment can reduce HbA1c level by 0.4% within 3 months, thus improving periodontal status while attaining diabetes control. The insulin receptor is activated while someone is fasting, which may result in a migraine attack. It was discovered that migraineurs' glucose plasma concentrations were substantially greater than those of controls.[6]

CONCLUSION

This narrative review concludes that periodontal disease and chronic migraine shares common biomarkers and inflammatory mediators. Hence, there is strong correlation between PD and migraine chronification. However long term studies with increased number of participants should be conducted to confirm this correlation.

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