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Periodontal disease as a potential factor of migraine chronification

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ABSTRACT

Migraine is a hereditary constitutional base disorder, which is characterized by recurrent episodes of headache pulsatile characteristics associated with photophobia/phonophobia, nausea and/or vomiting. The main complication in migraine is the chronicity of the process, now recognized as a chronic migraine. Although pathogenic mechanisms that may influence the pathophysiology of migraine and its possible chronicity are not fully understood, previous studies have shown in patients with migraine molecular alterations of systemic inflammation, neurogenic inflammation, endothelial dysfunction, innate immunity, dysfunction of matrix proteases and blood-brain barrier. Periodontal disease is an inflammatory lesion caused by bacteria. After the bacterial infection begins, an immune response that will be responsible for individual susceptibility appears. More advanced forms of periodontitis have demonstrated molecular alterations of inflammation, endothelial dysfunction, dysfunction of matrix proteases and innate immunity, similar to those observed in migraine. Furthermore, the main molecular mediators of neurogenic inflammation related to activation of the trigeminovascular system, which are characteristic of migraine, are overexpressed in gingival crevicular fluid and mucosa in patients with periodontal disease. Hypertension, hypercholesterolemia, insulin resistance, stroke or coronary artery disease are comorbidities that periodontal disease and migraine could share. Therefore, several mechanisms and hypotheses could explain the possible association between both diseases. However, epidemiological and molecular studies will be necessary to provide a better understanding of this potential association, which could be implicated in the chronification of migraine.

Introduction

Migraine is a type of primary episodic headache that is defined by its clinical features, including recurrent episodes of unilateral high-intensity pulsatile headache that are aggravated by habitual physical activity and usually accompanied by hypersensitivity to light and noise and vegetative symptoms such as nausea or vomiting [1].

In migraine two entities are distinguished, namely migraine without aura and migraine with aura. The concept of aura could be defined as the transient neurological visual, sensory or language symptom that may precede or accompany the headache [2].

Categorization of episodic migraine depends on the number of headache that a patient experiences. According to the International Headache Society, when the headache appears for ≥15 days per month for more than 3 months (at least 8 days should meet criteria for migraine) chronic migraine would be the correct diagnostic [2].

In the Western world, the overall annual prevalence of migraine is 11% (18% in women and 6% in men), with prevalence peaks (25% in women) in the most productive years of adulthood (from 25 to 55 years) [3,4].

Although chronic migraine is less prevalent than episodic migraine, the main complication in episodic migraine is the chronicity of the process [5].

Various risk factors for migraine chronification have been identified such as overuse of acute migraine medication, ineffective acute treatment, obesity, depression, low educational status and stressful life events [6].

Periodontal disease (PD) is a common inflammatory and infectious disease among the adult population [7]. After bacterial infection begins, an immune response will be responsible for individual susceptibility [8].

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In recent years, PD has been linked to various systemic diseases such as cardiovascular and cerebrovascular diseases, rheumatoid arthritis, diabetes mellitus, dementia and adverse pregnancy outcomes [9–14].

Three basic mechanisms have been postulated that could play a pivotal role in these interactions: metastatic infections, inflammation and inflammatory injury, and adaptive immunity [15].

Although specific association between PD and migraine has not been yet investigated, more advanced forms of PD have shown molecular alterations of inflammation, endothelial dysfunction, matrix protease dysfunction and innate immunity, similar to those observed in migraine [16–18].

Plausibility of a potential relationship between periodontal disease and migraine

Molecular alterations of inflammation

Numerous studies have shown that periodontal patients have increased levels of inflammatory mediators including increased levels of C-reactive protein (CRP), interleukin-1 (IL-1) and IL-6, tumor necrosis factor-alpha (TNF-α) compared to healthy controls [16,17]. In migraine, the same pattern of inflammatory markers has been observed in the systemic circulation [19]. These cytokines are proinflammatory and have also been implicated in vascular dysfunction [20].

Alterations of endothelial function

Some studies have suggested that patients with migraine have impaired endothelial function [21,22]. Likewise, PD produce a chronic low-grade state of systemic inflammation and, therefore, causing endothelial dysfunction [18].

Elevated levels of fibrinogen indicate systemic inflammation and may also damage blood vessel walls causing smooth muscle proliferation and migration [23]. Certain studies reported an increase of von Willebrand factor and fibrinogen levels in migraineurs compared to controls [24–26]. Similarly, several studies found higher concentrations of fibrinogen in patients with PD than in healthy subjects [27–29].

Endothelial progenitor cell (EPC) have a key role in endothelial regeneration and repair of injured vessels. The EPCs were reduced in migraine compared to controls and its function was also reduced in patients with migraine, showing a reduced migratory capacity and increased cellular senescence [30]. Furthermore, moderate or severe PD was associated with increased levels of circulating EPCs [31].

Pentraxin-3 (PTX-3) is one of the PTXs with a C-terminal and long N-terminal domain which appears to be specific to vascular damage [32]. It was shown that PTX-3 levels rise during a migraine attack [33]. Similarly, in patients with PD, PTX-3 concentration was found to be higher in gingival crevicular fluid and plasma than in healthy subjects [34].

Matrix protease dysfunction

Biomarkers associated [i.e., matrix metalloproteinase-9 (MMP-9)] with vascular repair/remodelling have also been linked with migraine. It is believed that MMPs may play a pivotal role in periodontal destruction [35]. In addition, plasma levels of MMP-9 are significantly higher in migraineurs than in control subjects [36].

Immune responses

The pathogenesis of migraine involves immune-mediated mechanisms in the vascular endothelium. Toll-like receptors (TLRs) are master regulators of innate immune function and are involved in the activation of inflammatory responses in the brain [37]. TLRs have been implicated in host innate immune responses to periodontopathogenic bacteria and in the activation of adaptive immunity. Moreover, dysfunctional host immunity induced by periodontal pathogens could contribute to the progression of PD [38].

Increase of mediators of neurogenic inflammation

In migraine, the neurogenic inflammation involves two different processes: vasodilation and increased vascular permeability [39]. These phenomena are modulated at a molecular level by the release of a series of neuropeptides [i.e., substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP)] [39].

Studies investigating the distribution of neurochemical markers in tissue obtained from gingivitis and PD affected sites showed that the tachykinins, SP and NKA were significantly elevated in PD [40]. However, they failed to detect CGRP in PD sites. It is suggested that selective degradation of CGRP, but not SP or NKA, could serve to enhance the proinflammatory effects of the tachykinins in periodontal inflammation [41].

Comorbidities associated with migraine and periodontal disease

Epidemiological (i.e., longitudinal, cross-sectional and case-control studies) data have shown a strong association between PD and migraine with some medical conditions.

Hypertension

Epidemiological evidence has reported a significant association between migraine and hypertension. Patients with chronic migraine are more likely to be hypertensive than patients with episodic migraine [42]. An increased prevalence of migraine and other headaches with auras was observed with hypertension [43]. Furthermore, the presence of hypertension increases the risk of arterial damage in migraine patients [43].

A recent systematic review described the potential influence of PD on hypertension with a higher risk of hypertension especially for severe PD [44]. This relationship may be explained by common risk factors or by dissemination of infectious and inflammatory components from periodontal lesions through bloodstream, immune response or glucose and lipids metabolism [45].

Hypercholesterolemia

It has been demonstrated that patients with migraine had higher levels of total cholesterol and low-density lipoprotein (LDL) cholesterol compared to those without migraine [46]. The authors found a significant association of total cholesterol with migraine in elderly men after adjustment for confounding variables.

It is considered that high fat diet produces platelet aggregation, which implies higher levels of prostaglandin and lower levels of serotonin, leading to vasodilation, which is an aetiological factor of migraine [47].

Presence of hypercholesterolemia or dyslipidemia in patients with migraine may increase the risk of vascular wall injury. Hypercholesterolemia is associated with an increase in endothelial