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Peri-Implantitis And Brain Inflammation: A Putative Axis

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Abstract:
Peri-implantitis (PI) is a chronic inflammatory disease of infectious origin that affect dental implants and this condition is the dominant reason for implant failure. At the moment, periodontitis which also is caused by microbial dysbiosis has been related to several types of systemic disorders such as diabetes mellitus, cardiovascular diseases Alzheimer's disease, Parkinson's disease and others. Based on the facts that the dysbiosis observed in periodontitis also be observed in PI, once the main types of bacteria (Porphyromonas giginvalis, Fusobacterium nucleatum, Treponema denticola and other) and their products are observed in the periodontitis/PI is possible which this type of rehabilitation (using dental implants) may be a risk to development and/or exacerbating systemic disorders, as well as neuroinflammation and reactive gliosis contributing with development or exacerbating neurological disorders.

Key Word*: Nervous System; Neuroinflammation; Periodontitis; Peri-Implantitis; Systemic Disorders.*

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I. Mini Review

Peri-implantitis (PI) is a chronic inflammatory disease originating from an infection. Affecting dental implants, it is the main reason for implant failure [1,2]. In patients who were submitted to dental implant rehabilitation and are potential candidates for the development of this disease, it is possible, at first, to observe peri-implant mucositis, a clinical condition characterized by inflammatory lesions of the mucosa around the implant without loss of supporting peri-implant bone, whose characteristics include redness, swelling, bleeding on gentle probing, and suppuration [3]. If no regular supportive peri-implant therapy is carried out to deal with the peri-implant mucositis, a worsening of this condition may lead to peri-implantitis [3]. PI is characterized by peri-implant mucositis clinical manifestations coupled with bleeding on probing and/or suppuration, in addition to progressive bone support loss [3,4].

Similar to PI, periodontal diseases are characterized by microbial dysbiosis [4,5]. In a susceptible individual, this pathological condition may result in the destruction of the supporting bone with the potential for tooth loss [4,6]. Substantial scientific evidence indicates that periodontitis has a plausible relationship with the development of several systemic alterations, such as diabetes mellitus, cardiovascular diseases, intestinal alterations, respiratory tract infection and pneumonia, pregnancy outcomes, and others [7-10]. This pathological disturbance of mouth health can be associated with central nervous system pathologies due to the existence of an oral-brain axis of communication, which may trigger the development of neuroinflammatory or neurodegenerative diseases or potentiate them [8].

As described above, periodontitis is an infectious bone-resorptive chronic disease caused by the dysbiosis of the periodontal microbiota that causes the first local immunoinflammatory response. Studies have observed *Porphyromonas Giginvalis* in the bloodstream of patients with or without periodontitis after teeth brushing, flossing, or chewing food. When bacteria are found in the bloodstream, organs such as the liver, for example, start inflammatory phase responses, increasing pro-inflammatory cytokines that can penetrate into the brain through the breakdown of the blood-brain barrier (BBB), altering its physiological functions [8]. Moreover, the neuronal membrane receptors in the trigeminal nerve endings (for instance TRLs, Toll-Like Receptors; TRP transient receptor potential), which are present in the periodontal tissues of upper and lower teeth, could be an "open door" for the bacteria and its products, causing that "periodontitis to arrive at the brain" [8]. Likewise, pathogenic bacteria can move along the axon or dendrites of the neuron through vesicular trafficking [8]. If both happen, the neuron will respond by producing pro-inflammatory cytokines (interleukin -1β [IL-1 β], interleukin-6 [IL-6], and

tumor necrosis factor- α [TNF-α], for instance) and start an inflammatory response in the trigeminal ganglion [8]. At this point, it is worth noting that in this ganglion there are glial cells (astrocytes and microglial cells) capable of contributing to the initial inflammatory response and, potentially, to damage nervous tissue [8]. Finally, pathogenic bacteria with the ability to inhibit the phagosome-lysosome complex and/or its products can arrive in the brain via lymphatic system (lymph nodes of the mouth and/or the III and IV cerebral ventricles) [8] [Figure 1].

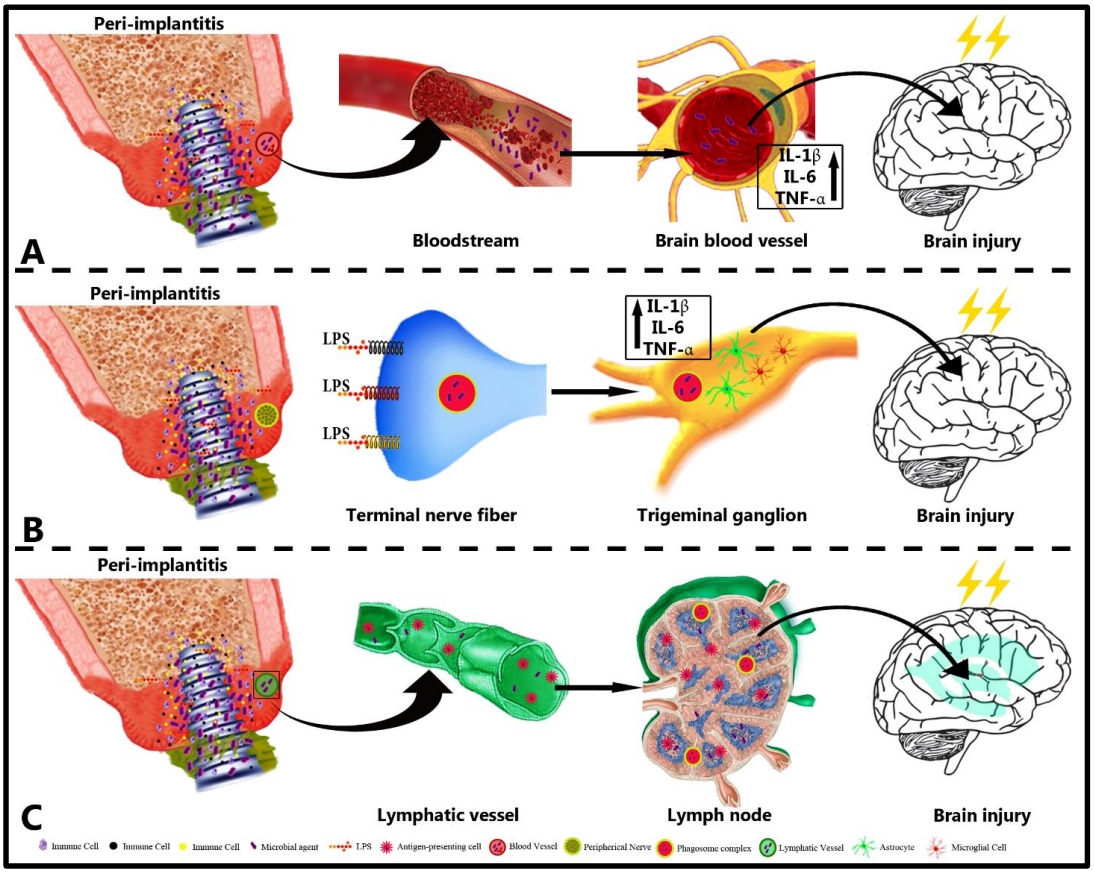

Figure 1. Putative brain inflammation after the presence of peri-implantitis (PI). In **A**, the presence of bacteremia could induce functional changes in cells of blood-brain-barrier (BBB) like astrocytes and microglial cells which produce pro-inflammatory cytokines (IL-1β, IL-6 and TNF, for instance). If this situation is observed, a breakout of the BBB could occur and then the inflammation induced by astrocytes and microglial cells could arrive into the brain, induce brain inflammation, affect neuronal function and, probably, contribute to neurodegenerative diseases like Alzheimer's disease and other. In **B**, the terminal fibers from the trigeminal nerve which is responsible for sensitive innervation of tissues from the mouth have various surface receptors that could recognize lipopolysaccharide (LPS). In the presence of interaction between LPS receptors, the neuron could produce IL-1β, IL-6, and TNF-α in the trigeminal ganglion. Besides that, the trigeminal ganglion has astrocytes and microglial cells which can recognize bacteria and also produce pro-inflammatory cytokines. In the same way, some types of bacteria can inhibit phagosome-lysosome complex and, through vesicular trafficking, can move along the axon of the neuron and then, an inflammatory response also could be observed. As described above, the presence of pro-inflammatory cytokines in the trigeminal ganglion could contribute to brain inflammation. In **C**, the bacteria and/or its products from PI could penetrate into the lymphatic vessel from periodontal tissues, recognize by antigen-presenting cells and start the immune response. Should this situation occur, cells from the immune system can arrive at the brain via III or IV ventricle. Another hand, if the bacteria have the ability to inhibit the phagosome-lysosome complex can arrive at the secondary lymph node and also achieve in the brain via III or IV ventricle. Abbreviation: TNF-α, tumor necrosis factor - alpha; IL-6, interleukin 6; IL-1β, interleukin 1 beta.

Considering the above, in addition to the findings of previous research, it is possible to suggest a relationship between periodontitis and neuroinflammation [8,9]. When the patient loses one or more teeth, oral rehabilitation can be done by using dental implants that promote stability to mastication, comfort, improve aesthetics, and more. This type of rehabilitation is the first choice of most patients in the dental office [5].

According to the American Academy of Implant Dentistry (AAID), 3 million Americans citizens have implants, and this number may grow by 500,000 per year [5]. However, it is necessary to discuss that dental implants can be infected by several types of bacteria, and if no steps are taken to deal with this issue, peri-mucositis and/or PI may develop [3]. In recent years, PI has been observed in 28%–56% of patients submitted to dental implants and in 12%–43% of their implant sites [5]. It is important to mention that the same oral environment, anatomy, and physiology have been observed in the oral cavity of patients with healthy teeth and periodontitis, whether they had healthy or unhealthy implants, respectively [3,8]. Based on the fact that the dysbiosis observed in periodontitis can also be observed in PI, due to the fact that the same types of bacteria (*Porphyromonas Giginvalis, Fusobacterium Nucleatum*, *Treponema Denticola*, and others) and their products are observed in periodontitis and PI [5], this type of rehabilitation (using dental implants) may be a risk to the development and/or exacerbation of systemic disorders, as well as neuroinflammation and reactive gliosis, as observed in periodontitis. This could contribute to the development of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis (ALS) via the mouth-to-brain axis (lymphatic, nervous, or circulatory systems), widely discussed in regard to periodontitis.

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