Periapical Disease and the Prefrontal Cortex.

Is there a Relationship between Calcium-Binding Protein and Neurodegenerative Diseases?

Doença Periapical e Côrtex Pré-Frontal. Existe uma Relação entre a Proteína de Ligação ao Cálcio e as Doenças Neurodegenerativas?

Enfermedad Periapical y la Corteza Prefrontal: Existe una Relación entre la Proteína Fijadora de Cálcio y las Enfermedades Neurodegenerativas?

Gesttler Willian Lattari TESSARIN
University Center North Paulista (UNORP), São José do Rio Preto, SP, Brazil
https://orcid.org/0000-0002-7355-0562
Rodrigo Martins dos SANTOS
Multicenter Post-Graduate Program in Physiological Sciences, SBFiS, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0002-5122-275X
Renato Felipe PEREIRA
Multicenter Post-Graduate Program in Physiological Sciences, SBFiS, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0002-4696-4070
Maria Sara de Lima Coutinho MATTEA
Multicenter Post-Graduate Program in Physiological Sciences, SBFiS, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0003-2288-708X
Thais Verônica Saori TSOSURA
Multicenter Post-Graduate Program in Physiological Sciences, SBFiS, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0003-1708-4071

Abstract

Apical periodontitis (AP) or periapical lesion (PL) is an inflammatory disease that causes pain, loss of bone and destruction of other tissues of teeth support. This condition could be caused by caries, dental trauma and/or periapical microleakage which is regulated by the immune system or inflammatory response. Several analyses have shown that endodontic infection can cause systemic alterations like stroke, insulin resistance, cardiovascular diseases and to contribute to the appearance of neurodegenerative disorders. The prefrontal cortex (PIC), positioned in the most anterior region of the brain, is essentially involved behavioral abilities, intellectual roles, cognition, learning and other functions. Neurons with laminar distribution in the PIC, especially in the lower layers express several types of calcium-binding proteins (CaBPs) like parvalbumin, calbindin and calretinin that are involved in calcium buffering into the brain (CNS). These proteins are co-localized with GABAergic neurons, main inhibitory cells into the brain. Piece of evidence has pointed out a relationship between apical periodontitis and neurodegenerative diseases where microorganisms and/or toxins produced in the teeth infection can penetrate the bloodstream, infiltrate the blood-brain barrier limit and active astrocytes and microglial cells in the central nervous system (CNS) and increase the releasing of pro-inflammatory cytokines promoting pyramidal and non-pyramidal neuronal degeneration. Thus, is there a relationship among apical periodontitis, oral hygiene and prefrontal cortex and neurodegenerative disorders?

Descriptors: Calcium-Binding Proteins; Inflammation; Neurodegenerative Diseases; Periodontal Diseases; Pre-Frontal Cortex.

Resumo

A periodontite apical (AP) ou lesão periapical (PL) é uma doença inflamatória que causa dor, perda óssea e destruição dos tecidos de suporte dos dentes. Esta condição pode ser causada por cárie, traumas dentários e/ou microinfilação periapical, sendo regulada pelo sistema imunológico ou resposta inflamatória. Diversas análises mostraram que a infecção endodontica pode causar alterações sistêmicas como acidente vascular cerebral, resistência à insulina, doenças cardiovasculares e contribuir para o aparecimento de doenças neurodegenerativas. O córtex pré-frontal (PIC), posicionado na região mais anterior do cérebro, envolve essencialmente habilidades comportamentais, papéis intelectuais, cognição, aprendizagem e outras funções. Neurônios com distribuição laminar no PIC, especialmente nas camadas inferiores, expressam vários tipos de proteínas ligadoras de cálcio (CaBPs) como parvalbumina, calbindina e calretinina que estão envolvidas no tamponamento de cálcio no cérebro (SNC). Estas proteínas são co-localizadas com neurônios GABAérgicos, principais células inibitórias no cérebro. Evidências apontam para uma relação entre periodontite apical e doenças neurodegenerativas, onde microrganismos e/ou toxinas produzidas na infecção dos dentes podem penetrar na corrente sanguínea, infiltrar-se no limite da barreira hematoencefálica e ativar astroctos e células microgliais no sistema nervoso central (SNC), aumentando a liberação de citocinas pró-inflamatórias, promovendo degeneração neuronal piramidal e não piramidal. Assim, existe relação entre periodontite apical, higiene bucal, córtex pré-frontal e distúrbios neurodegenerativos?

Descritores: Proteínas de Ligação ao Cálcio; Inflamação; Doenças Neurodegenerativas; Doenças Periodontais; Córtex Pré-Frontal.

Introduction

Apical periodontal (AP) or periapical lesion (PL) is an inflammatory disease that causes pain, bone loss and other tissues of dental support\(^1\). Initially, this inflammatory condition is caused by microbial infections...
Neurotransmitter y-aminobutyric acid (GABA) and its receptors

The y-aminobutyric acid (GABA) is the main neurotransmitter in the mammalian brain that inhibit excitatory synapses. This discovery was reported in 1950 and after various researches revealed that this neurotransmitter participates in most neurophysiological processes like memory, vigilance, muscle tension and anxiety. It works through the inhibition, the interneurons that express GABA can actively act and to promote the brake on excitatory signaling into the cerebral cortex, including the PfC cortex, preventing the uncontrolled excitation from afferent structures and then cause the equilibrium or balance between inhibition and excitation stimulations.

In another hand, this neurotransmitter has been linked with cerebral disorders, including alterations in behavioral aspects, pain, sleep, schizophrenia, epilepsy, Alzheimer’s disease and autism spectrum disorders. This relationship between GABA and several types of disorders could be interconnected because the decrease of GABA levels into the several regions of the brain, including the PfC, promote the decrease of interactions between GABA and its receptors and the hyperpolarization of presynaptic neurons is abrogation by a decrease in chloride (Cl⁻) influx into the cell, like observed by Auger and Floresco that analyzed by infusion of bicuculline, a GABA R antagonist, the disruption of memory and intellectual flexibility in multiple species. In the same way, in vivo analysis in autistics patients, the reduction of GABA and its receptors, like GABA R, it was observed the reduction in gamma wave with great oscillations.

In primates, the administration of bicuculline also revealed wich the circuit of pyramidal and non-pyramidal neurons in the PfC reduced the GABA signaling and severely limited the neurophysiologic ability of this circuit and promoted inability of working and relay correct motor commands with precision. Currently, clinical trials have been reported that the use of synthetic GABA drugs, for instance an agonist benzodiazepine, the lorazepam, modulate the glutamatergic signaling showing a potential treatment in psychosis and working memory in schizophrenic patients and situations of epilepsy in autistics patients. It’s important to mention that the PfC also has a laminar and columnar distribution of neurons. In the laminar distribution (layers I-VI), the cortical layer IV is rich in inhibitory GABAergic interneurons. These interneurons receive input from bioaminergic nuclei in the brain stem and "advance" to

(predominantly due to gram-negative anaerobic bacteria) within endodontic root induced by caries and/or dental trauma and/or periapical microleakage. Firstly, this condition is regulated by the host immune and/or inflammatory response. The presence of periapical inflammation actives the immunologic system stimulating several immune factors, like antibodies, complement system, arachidonic acid metabolites and pro-inflammatory cytokines. Recently, several studies observed that inflammation of oral cavity can be a relationship with systemic disorders as diabetes cardiovascular and renal diseases, preeclampsia, cirrhosis and also neurological disorders.

The brain has several functions as learning, speaking, cognitive control, spatial and visual perception, memory, language and others. In special, the prefrontal cortex (PfC), positioned in the most anterior portion of the brain, can be basically divided into three main regions: orbital (orbitofrontal, OfC), medial (MPFC) and lateral. This portion of the brain has structural and functional heterogeneous regions with several distinct neurochemical areas that possibility various behavioral and cognitive features, attention, association, working memory, sequencing of tasks, expression of emotional state and learning. In addition, in vivo studies using neuroimaging techniques has been evidenced that different sections of the PfC are activated in different task demands or information processing.

In the cerebral cortex, gamma-aminobutyric acid (GABA) is the main inhibitor molecule of cortical excitatory neurons from the brain that has a role in modulation in the local neurotransmitter system, controlling the emotional and cognitive processes. It’s important to mention that approximately 30% of all synapses in the central nervous system (CNS) are interconnected by GABAergic interneurons and these types of cells which promote inhibitor synopsis into the brain also express calcium-binding protein (CaBPs), particularly parvalbumin (PV) and calbindin D-28k (CB). As described above, several studies have shown that AP may influence in systemic disorders promoting alterations in several tissues like skeletal muscle, cardiovascular blood vessels, bone, hepatic tissues, liver and others tissues. Neurological disorders linked with inflammatory alterations caused by AP also has been shown and proven in several studies. Thus, is there a relationship among periodontal disease, CaBPs and cerebral disorders as Alzheimer’s and schizophrenia diseases?
provide inhibition to local pyramidal excitatory neurons principally in cortical layers III and V. GABAergic interneurons have been implicated in the executive deficiencies of neurological diseases and may represent one of the main targets of atypical neuroleptics diseases. In this point of view, the neuronal circuits present in the PfC is widely controlled by interactions of GABAergic neurons which control several types of excitatory neurons located in all layers of the cerebral cortex being the interaction between GABAergic neurons – GABA receptors – excitatory neurons the important equilibrium to the normal of many types of functions performed by the brain and then, the maintenance of this circuits along the life can contribute to a regression of emergence of various types of neuropsychiatric disorders.

- **Calcium-binding proteins (CBPs)**

  Ions calcium (Ca$^{2+}$) are essential for the homeostasis in neurons contributing to their functions and survival. Furthermore, intracellular Ca$^{2+}$ signaling in neurons and other types of cells is important to control gene transcription, membrane excitability, in release of several neurotransmitters and many other cellular procedures, including synaptic plasticity. Calcium-binding proteins (CBPs) are a large group of proteins consisting of over 240 subtypes, involved in several roles in the brain as regulation of the level of calcium ion, neuronal plasticity, brain development and function, neuroprotection, aging, memory, synapse formation and others functions. Among the members of CBPs, calbindin-D28k (CB), parvalbumin (PV) and calretinin (CR) are highly expressed in neurons of the CNS and the CBPs are colocalized in approximately 90% neurons $\gamma$-aminobutyric acid (GABA) positive. CBPs are expressed in pyramidal and non-pyramidal neurons distributed in several laminar and columnar regions into the brain, including the PfC in several primates human and non-human and rodents. Neurons that express PV, CB and CR which also express GABA are distributed in all layers of the PfC of human, rats and mice with major density in layer IV in a dysgranular and granular cortex. In the same way, in capuchin monkey (Sapajus apella) this situation also is observed (unpublished data).

Recently, a lot of evidence suggests that AP presents a relationship with various types of neurological disease as stroke, amyotrophic lateral sclerosis, Alzheimer and Schizophrenia’s diseases, depression and moods alterations showing that systemic neuroinflammatory caused by AP can result in structural and functional disturbances into the brain, including alterations in neurotransmitters like GABA presents in pyramidal and non-pyramidal neurons and cell metabolism, basically associating this condition with an increase of inflammatory cytokines into the cerebral parenchyma and stroma. To support this data, an animal model of sepsis showed an increase of tumor necrosis factor alpha (TNF-$\alpha$), interleukin 1 beta (IL-$\beta$), interleukin 6 (IL-6), and interleukin 10 (IL-10) expressions in the PfC and hippocampus with PV positive interneuron loss linking this phenotype with cognitive impairments because the gamma oscillations have been associated with altered function of PV positive interneurons and neurological and/or psychiatric disorders with a manifestation of deficits in memory activity and executive functions. This data has been confirmed in other studies of Alzheimer’s disease, epilepsy, depression and autism (to review). Thus, of a neurophysiologic view, the CBPs in neurons are essential to several types of functions and the imbalance of this family of proteins could promote the accumulation of calcium ions into the neurons and provide cell death and then contribute to a decrease of inhibition of excitatory neurons.

- **Apical periodontitis, neuroinflammation and neuronal loss**

  Several types of gram-positive, gram-negative, anaerobic and aerobic microorganisms are present in the oral cavity when the patient has good mouth hygiene. In this way, various tissues into the oral cavity are a perfect local to proliferate bacterial microorganisms and a biofilm form. In several situations, such as the imbalance between the host and the infectious agents that constitutively inhabit the oral cavity, several carious lesions may occur, which, if left untreated, may cause the appearance of endodontic infections inhabited mainly by Prevotella intermedia, Streptococcus, Peptostreptococcus, Fusobacterium, Porphyromonas, Eubacteria and Parvimonas. If the endodontic treatment is not successfully performed, the appearance of periapical abscesses can lead to the emergence of other types of microorganisms such as Fusobacterium nucleatum, Prevotella intermedia, Peptostreptococcus micros, Eubacteria, Peptostreptococcus anaerobius. Pieces of evidence from several lines of investigation have pointed out to relationship between periodontics with neurological diseases, as precede described. In special, the presence of periodontal disease...
causes inflammatory signaling where the toxins that are produced in this infection and/or the bacteria can be the bloodstream and reach the brain across the blood-brain barrier (BBB)\(^{96}\). In the same way, periodontal disease increase circulating levels of pro-inflammatory cytokines, for example, TNF-\(\alpha\), IL-1\(\beta\), IL-6, interleukin-8 (IL-8) and IL-10 induced by LPS (lipopolysaccharides) from periodontal microorganisms observed into the oral cavity and/or infiltrating to the bloodstream\(^{91-93}\). Between several virulence factors from gram-negatives bacteria is the lipopolysaccharide (LPS) constitutively presents in cellular wall leave in vesicles and/or after its disintegration\(^{94}\).

The LPS is mainly recognized by Toll-like 4 receptor (TLR4), a receptor localized in the plasemmma of immune cells and this interaction induces the activation of innate and realizes the induction of inflammatory responses\(^{95}\). The TLR4 in express in different types of cells (monocytes, macrophages and others) and tissues\(^{96}\), performing an important function on the development of chronic alterations linked with obesity and insulin resistance\(^{97,98}\). The TLR4 recognizes the LPS and promotes the synthesis of pro-inflammatory cytokines as TNF-\(\alpha\), IL-1\(\beta\), IL-6, IL-8 and interleukin-12 (IL-12) which in turn act as endogenous inflammatory mediators through interaction with receptors found in different target cells. This situation between periodontitis and systemic inflammation was observed in analysis using patients with periodontitis where the levels of pro-inflammatory C-reactive protein (CRP) and leptin in serum were increased\(^{99}\). Besides that, in various organs and tissues was observed inflammation with an expression of pro-inflammatory mediators and reduced insulin resistance in adipose tissue as well as increased micro-RNA and TNF-\(\alpha\) level in an animal model with administrations of \textit{Porphyromonas gingivalis}\(^{100}\).

Specifically, there are increasing studies supporting the relationship between oral infections and cerebral disorders\(^{14,101,102}\). Kamer et al.\(^{103}\) proposed that the inflammatory molecules from periodontitis into the CNS could promote the development of Alzheimer’s disease. This inflammatory situation from the oral cavity may be to promote inflammation stress into the brain and cause microglial activation, astrogliosis, loss of neuronal synapses and neuronal degeneration promoting also a diminution of essential neurotransmitters like the GABA\(^{85,104}\). It is important to mention that the mechanism by which pro-inflammatory molecules from periodontitis arrive and increase in the brain molecular inflammatory involves two pathways: the blood /lymphatic circulation and/or the neural pathways\(^{104}\). Ilievski et al.\(^{14}\) observed neuroinflammation, neurodegeneration, microgliosis and astrogliosis after oral administration of \textit{Porphyromonas gingivalis} in C57BL/6 mice. Zhang et al., \(^{16}\) also reported the activation of astrocytes and microglia cells in the cerebral cortex and hippocampus after intraperitoneal injection of \textit{Porphyromonas gingivalis} in C57BL/6 mice inducing cognate disorders. In the same way, using an animal model (ApoE\(^{null}\) mice) of experimental periodontitis infected with \textit{Fusobacterium nucleatum}, \textit{P. gingivalis}, \textit{T. denticola} and \textit{T. forsythia} revealed the existence of DNA from \textit{P. gingivalis} showing that this bacteria can cross the BBB, to activated the inflammatory pathways and pyramidal neurons of the hippocampus were opsonized with and they were likely to have been vulnerable from activated complement system\(^{105}\). Thus, the presence of periodontal pathogens endotoxins and/or periodontal pathogens possibly can activate the inflammatory cascade and initiate the neuroinflammation\(^{44,90}\) and could be associated with cognitive disorders\(^{16,17,105}\).

Calcium-binding proteins (CBPs) is a group of proteins that are involved in several functions like the regulation of the level of calcium ion, neuronal plasticity, brain development and functioning, neuroprotection, aging, memory and others functions\(^{30,65,66,106,107}\). On the other hand, the CBPs also are involved in cerebral pathological situations such as Alzheimer’s and Parkinson’s diseases, schizophrenia and bipolar disorder\(^{69,108,113}\). In the cerebral cortex, the main inhibitory neurotransmitter is gamma-aminobutyric acid (GABA) and approximately 25% of all neurons of the neocortex of the monkey’s brain are GABAergic neurons and they also express CaBPs, particularly PV and CB\(^{21,28,35,114}\). Recently, there is an increase in the number of evidence and hypothesis showing that disruption of inhibitory neurons in PfC could be involved in several features of neuropsychiatric and neurodegenerative disorders like schizophrenia and Alzheimer Diseases\(^{33,115-117}\). Schizophrenia, a psychotic alteration that affect approximately 21 million people around the world\(^{118}\). Schizophrenic patients present mainly changes related to altered energy metabolism, demotivation and control of cognitive modulation, such as memory loss and inattention\(^{119}\). The Alzheimer’s disease is a common situation of dementia and this condition can be caused by several situations as amyloid
plaque formation, accumulation of tau protein with oxidative and inflammatory brain damage in areas with advanced cognitive functions, that promote the progressive loss of the functions of the brain. In this way, the activation of the complement system (complement cascade), increase level of cytokine and chemokine expression can contribute to the development of this neurodegenerative disease.

In special point, the CB mRNA levels in schizophrenia increased in post-mortem brain samples as well as the number of CB positive neurons was increased in the frontal cortex of people with schizophrenia and in prelimbic areas of the PIC from animal models for schizophrenia, suggesting the compensatory mechanism to calcium buffer. On the other hand, studies have shown the decrease of CB positive neurons in the PIC of patients with schizophrenia. In the others conditions, neuronal diseases as Alzheimer’s disease, dementia and dementia studies also have been reported the decreased of CB cortical neurons. These findings relatively cannot explain the functional activity of the CaBPs, in special CB, in neuronal diseases with loss of GABAergic neurons, but the data of this study could help to understand, once this protein are differently distributed into areas of the PIC that are involved in cerebral diseases that present disturbance of the calcium.

Several scientific evidences have shown that PV also involved in neurodegenerative disorders. Volk et al. using quantitative PCR and in situ hybridization in postmortem samples of PIC from schizophrenia subjects observed lower PV positive neurons. In the same way, Beasley and Reynolds showed by immunohistochemical technique significant reduction of PV positive neurons in the PIC. Moreover, one study using a sample from human PIC showed that basket cells axonal that express PV protein are reduced and lower Pv mRNA expression. Thus, the decrease in PV positive neurons with loss of gamma waves in schizophrenic patients has been associated with deficits in memory and cognitive functions. The relationship among the altered function of PV neurons also confirmed in other neurological disorders like Alzheimer’s disease, epilepsy, autism, and depression.

In this way, the possible link between AP and development of Alzheimer’s and Parkinson’s diseases may be related with two points: 1) systemic inflammation can increase in the CNS the levels of pro-inflammatory cytokines development the neuroinflammation that cause astrogial and microglial activation induced by AP; 2) neuroinflammation performed by invasion of periodontal pathogen and/or their inflammatory components (for instance: endotoxin, LPS, virulence factors and others) into the brain that also can the cause similar situation of neuroinflammation. In this way and as described above, the presence of the neuroinflammation into the brain caused by bacterial and/or toxins from the AP can activate the astrocytes and the abnormal calcium and glutamate homeostasis in reactive astrocytes can contribute to the pathogenesis of Alzheimer’s disease. For instance, studies using brains of animal models to Alzheimer’s diseases, the calcium-mediated signaling from astrocytes and gliotransmitter releases can be associated with disruption of β-amyloid peptide (Aβ), which indicates astrocyte dysfunction and contribute to the earliest neuronal deficits and loss in Alzheimer’s disease. Besides that, in mice model, excessive release of GABA by reactive astrocytes resulted in tonic inhibition of dentate gyrus granule cells in the hippocampus of Alzheimer mice model. Remarkably, inhibition of GABA or the use of pharmacological blockade of GABA transporters possibility the restore of synaptic and memory deficits. Moreover, in an animal model using a long-term ligation around the tooth, Li et al. observed alveolar bone loss and inflammatory alterations in dental support tissues with progressive cognitive deficits during a 12-month period as well as neuronal, synaptic disruption and glial activation. To support these data, using human or animal model analysis also were observed the presence of bacteria and/or toxins into the brain via peripheral nerves route. Therefore, reactive astrocytes increase the expression of GFAP and S100β proteins, pro-inflammatory cytokines and other neuromodulators that can promote the cascade event and contribute with the Alzheimer disease.

The health situation of the dental element and/or oral promotes a normal condition of dental support tissues and other oral tissues without range to the bloodstream of bacteria and/or toxins that cause a host immune/inflammatory response. Another hand, the presence of caries and/or other situations that cause endodontic infection can promote the liberation in the bloodstream of several microorganisms and/or theirs products that cross the blood-brain barrier and induce an astrocytic reaction and activation of microglial cells. This situation increases the liberation from astrocytes and microglial cells of cytokines pro-inflammatory into the prefrontal...
cortex contributing to a neuronal loss of several types, including the gabaergic pyramidal and non-pyramidal that express calcium-binding proteins constitutively, contributing with the appearance of neurodegenerative disorders like Alzheimer’s and Parkinson’s diseases and schizophrenia. Any portion of the prefrontal cortex with neurons expresses constitutively calbindin, calrethin and parvalbumin.

Similarly, it is possible that bacteria and/or toxins arrive in the cerebral cortex by bloodstream via, induce a brain inflammation with disorganization in dopaminergic neurotransmission in the basal nuclei and neuronal degeneration in the substantia nigra observed in situations of Parkinson’s disease with activation of astrocytes and microglia144-150, probably disclosing the similar condition described above where the systemic inflammation can increase in the CNS the levels of various pro-inflammatory cytokines that to disclose a neuroinflammation situation promoting astrogial and microglial activation induced by AP and the neuroinflammation performed by direct invasion of periodontal pathogen and/or their inflammatory components into the PIC can cause pyramidal and non-pyramidal neuronal loss, specifically that have presents constitutive CaBPs, essential molecules involved in several important functions of this type of cells. Thus, the neuroinflammation could contribute to several types of neurological disorders where is observed neuronal loss117.

**FINAL CONSIDERATION**

The CNS are considered the place with the right protection in the body. However, several studies have been shown the relationship with oral diseases and systemic disorders including neurological disorders.

Periodontitis is very common in a great portion of the global population and the bacterias and/or toxins from this disease can cause a series of immune responses that disclosing an inflammatory cascade in the body.

In the brain, this situation is not different from the others tissues and then the neuroinflammation can promote the neuronal loss and activation of astrocytes and neuroglia and the mainly calcium-binding protein (CaBPs) may be involved in neurodegenerative disorders like Alzheimer, schizophrenia and others neurodegenerative diseases. These relationships can be interconnected by fluctuations in levels of calcium ions that caused alterations in cerebral homeostasis and neurodegeneration in neurons and/or interneurons GABAergic positive to parvalbumin (PV), calretinin (CR) and calbindin D-28k (CB) that are involved in several functions into the brain mainly in inhibitory synopsis showing a possible interrelation among periodontal/periapical infections and neurodegenerative diseases. Thus, periodontitis treatment using conventional treatment may be a benefit to prevent several types of brain diseases, improve the Alzheimer’s and Parkinson’s conditions or extend the onset of the disease, improving the quality and expectancy of life in the global population.

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CONFLICTS OF INTERESTS
The authors declare no conflicts of interests.

CORRESPONDING AUTHOR
Gestter Willian Lattari Tessarin
University Center North Paulista, UNORP
Ipiranga Street, 3460 - Jardim Alto Rio Preto
15020-040 São José do Rio Preto - SP, Brazil
E-mail: gestter@unorp.br

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