

# Periodontitis and stroke

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## Abstract

There are various forms of periodontitis characterised as an inflammatory disease with more or less expressed alteration of genetic immunological components and associated with local as well as psycho-social factors. Presence of chronic destructive inflammation in the mouth – a region with rich blood supply, contributes to escape of bacteria, their virulent factors and various pro-inflammatory cells, cytokines and immunologically active substances into the blood stream and their subsequent penetration into different organs and tissues, where they continue in their harmful destruction. Atherosclerosis of cerebral vessels and its consequences resulting in ischaemic stroke are the most frequent cause of acute strokes. Today's knowledge and studies of etiopathogenesis of vascular atherosclerosis present the atherosclerotic process of vascular walls as metabolic, infectious and immunological process, which progressively obliterates vascular lumen and creates conditions for acute and chronic vascular events in various regions. Inflammation is a source of chronic and acute infections in often distal organs and tissues as a risk factor of an atherosclerotic vascular process. This review study deals with epidemiological and etiopathogenetic association between chronic periodontitis and a stroke. A special emphasis is put on explanation of possible relations between an oral infection and stimulation of pro-atherogenetic mechanisms. The second part of the paper deals with principles of treatment in patients after stroke.

## INTRODUCTION

A stroke or cerebrovascular accident is an acute disease characterized by loss of cerebral functions caused by brain ischemia. Brain ischemia has two very frequent causes. The first one is a blockage of vascular lumen due to an atherosclerotic process, thrombus or embolic stroke. In small cerebral vessels, the atherosclerotic process, expressed by cholesterol plaques up to completely developed atherosclerotic lesions, can gradually cause narrowing of the vessel lumen and initiate small thrombus formation. Similarly the lumen of small

vessels can be obliterated by atherosclerotic lesion particles. It is necessary to emphasize that the etiopathogenesis and risk factors of atherosclerotic process and vessel narrowing are very similar, even identical to the factors that cause coronary artery atherosclerosis and myocardial infarction (Wedro *et al.* 2013; Yoo *et al.* 2012). However it is necessary to mention the fact that there are several differences between intracranial and extracranial atherosclerosis (Jong-Ho *et al.* 2011; Kim *et al.* 2012). Blood flow disruption starts within 1 to 1.5 minutes of the start of cerebral tissue ischemia, which after three hours becomes irrevers-

ible. The state, in which atherosclerotic lesion particles or calc deposits are transported by blood circulation to the brain and then block some cerebral vessels, is called an embolic stroke. This state primarily develops during atrium heart fibrillation (Wedro *et al.* 2013). The given pathophysiological mechanisms are classified as ischaemic stroke and represent up to 87 per cent of all cerebrovascular accidents (Deb *et al.* 2010). A pathological state in which brain tissue is contused with one or several haematomas (blood escaped from vascular system), is described as a haemorrhagic stroke. Blood leaking from a broken vessel causes a swelling of cerebral tissue and increased intracranial pressure, which subsequently increases cerebral oedema and further brain tissue destruction in the closed cerebral cavity (Wang 2010).

A clinical picture of a sudden cerebrovascular accident is very variable and depends on which part of the brain is affected. Among the most common symptoms of a sudden cerebrovascular accident are headaches, vision defects, loss of vision, speech and writing defects, loss of physical orientation, uncontrolled urination etc. The most frequent risk factors are old age, heredity – a high concentration of the von Willebrand factor, high blood pressure, and cardiac diseases – arrhythmia, coronary artery disease, diabetes mellitus, high cholesterol and triglyceride concentrations in the blood, hyperhomocysteinemia, obesity, and lack of physical activity as well as chronic infections (Bongers *et al.* 2006).

Nowadays chronic destructive periodontitis is considered to be a risk factor for several systemic diseases, although no causal and etiopathogenetic associations are firmly stated, studies not having proved these associations. Among the most frequently observed and studied associations are diabetes, rheumatic arthritis, low birth pre-term born children and pre-eclampsia, respiratory diseases, kidney diseases and vascular atherosclerosis (Straka 2011a; Straka *et al.* 2012; Straka 2011b; Ležovič *et al.* 2012; Straka *et al.* 2011).

Strokes are one of the most frequent fatal diseases and cause up to 10 per cent of all deaths in the world. One of the most dangerous risk factors is the high age of patients. Up to two thirds of all strokes occur after the age of 65. Its incidence and prevalence is closely connected with genetically conditioned factors (WHO 2004; Bongers *et al.* 2006). According to NHANES III study, 19.1 per cent of the teeth of US patients have an index of attachment loss (AL) higher than 3.0 mm (Lee *et al.* 2006). From this fact, it can be concluded that various forms of periodontitis are the most frequent diseases in the world.

## EPIDEMIOLOGICAL ASSOCIATIONS BETWEEN STROKE AND PERIODONTITIS

Nowadays it is obvious that any chronic infection, including a dental one, is one of the risk factors of atherosclerosis in various geographic regions. In

nine longitudinal meta-analytical studies, a statistically important increase of cardiovascular diseases was stated in patients with periodontitis (Abolfazli *et al.* 2011). Development of atherosclerotic lesions in coronary and cerebral vessels has many common etiopathogenetic properties. Traditional risk factors have not explained the development of strokes in a sufficient way. In recent decades it has been found that a chronic infection can also increase the risk of strokes through various pro-inflammatory mechanisms, substances and markers – indicators of atherosclerotic lesions and strokes. There are dozens of different types of studies which have confirmed positive associations between inflammatory diseases of the periodontium and stroke. However some of them are limited due to their low number of studied cases, unequal diagnostic criteria for periodontitis or insufficient elimination of other risk factors (Grau *et al.* 2004).

Meta-analytical statistical methodology applied in electronic searching of studies revealed that in prospective studies patients with periodontitis had a 1.47 higher risk of development of ischaemic or haemorrhagic brain stroke. In retrospective studies, a risk of 2.63 / $P=$ .002/ (Sfyroora *et al.* 2012) was observed. In a group of 867,256 Korean men and women observed for 14 years, 28,258 brain strokes were registered, of which 5105 were fatal. As for pathological symptoms in dentistry, levels of lost teeth, diagnosed and treated hypertension, diabetes mellitus and smoking were all studied. Transient ischaemic attacks were divided into individual subtypes and an interaction between a decreased number of teeth, hypertension and haemorrhagic brain stroke was established, mainly in men (Choe *et al.* 2009). Periodontitis leads to tooth loss and increases the systemic inflammatory status of the organism, which can be associated with cerebral stroke. This was also confirmed by a review study in which the number of lost teeth, CRP and albumin concentrations, and the amount of white blood cells in 24,393 subjects were studied. Statistically important associations were detected mainly in numbers of missing teeth, stroke and serum concentrations of pro-inflammatory markers. Teeth loss was conditioned by race but not geographically (You *et al.* 2009). Associations between cerebral stroke and periodontitis probably demonstrate a dosed effect because at index values of clinical loss of attachment higher than 6 mm, the OR was 4.0 (Odds Ratio). It was stated that periodontitis is also an independent risk factor in a group of non-fatal strokes, mainly in subjects without hypertension, aged below 60 (Sim *et al.* 2008).

Some types of studies try to find connections between classical reasons and symptoms of both diseases. The National Health Interview Survey (NHIS) conducted in the USA, studied associations between dental visits and brain stroke prevalence in different groups of inhabitants. The conclusions of this study unanimously emphasize the importance of dental treatment and regular dental care and education, especially

in patients surviving after a brain accident (Sannosian *et al.* 2011). Increased neurological defectiveness has been detected in toothless patients and patients with advanced periodontitis who have suffered a stroke (Lowik *et al.* 2010).

## ETIOPATHOGENETIC ASSOCIATIONS BETWEEN INFLAMMATORY DISEASES AND SUDDEN CEREBROVASCULAR ACCIDENTS

### The role of chronic inflammation in development of atherosclerotic lesion

A periodontal pocket is a lesion of periodontal tissue which arises during osteolytic and proteolytic pathological processes. A primary etiopathogenetic factor is the presence of bacterial pathogens against which the immune answer of the appropriate subject is inadequate; its altered antibacterial protective function is unable to eliminate pathogens in the tissue. Periodontal tissues in subgingival regions are covered with oral biofilms filled with specific anaerobe gram-negative bacteria armed with rich virulent properties able to overcome mucous and tissue immunity and invade into surrounding periodontal tissues.

From the pathophysiological viewpoint, there is a certain shift in the concept of atherosclerotic lesion development. Today's opinions and evidence do not consider atherosclerosis to be a metabolic and degenerative process resulting in fibrous, adipose and calcified hardening of the vessel wall. Today's concept of atherosclerotic process presents it as an immune-metabolically controlled response of the vessel wall to various noxas; different inflammation types are considered to be the most important risk factors. Chronic periodontitis is associated with long-lasting anti-inflammatory local and total reaction. Its constituent is activation of both inflammatory mediators and cellulohumoral immunity, which increases the total pro-inflammatory status of the organism. Increased serum concentrations of immune active substances also influence the atherosclerotic process in cerebral veins and an acute infection can be a triggering mechanism for an ischaemic stroke (Ležovič *et al.* 2012; Grau *et al.* 1998; Dorfer *et al.* 2004; Kamel *et al.* 2012). Activated inflammation of the periodontium, including acute gingivitis, can increase several risk factors stimulating atherogenesis through the spread of periodontal pathogens (in a form of transient bacteraemia). Besides direct destabilisation of atheroma, thrombocytes become activated and coagulation factors concentrations increased, thrombi developed. *Porphyromonas gingivalis*, oral streptococci and staphylococci are important stimulators of coagulation mechanisms which activate the process of vascular atherogenesis (Ležovič *et al.* 2012; Grau *et al.* 1998).

A long-lasting chronic inflammation process in the periodontium stimulates (in immune active cells) production of the inflammatory mediators IL-1beta, TNF-

alpha, CRP, NF-kB, as well as the whole group of lipid pro-inflammatory substances, mainly PGE2 and the whole family of adhesive molecules and chemo-active factors. Some of the pro-inflammatory substances can pass also through the blood brain barrier (Borlongan *et al.* 2012). The incapability of the organism to eliminate periodontal bacteria and the subsequent formation of a pro-inflammatory mediator keep this local chronic inflammation active. The escape of bacteria and inflammatory substances can also initiate or stimulate an atherosclerotic process in the cerebral vessels (Grau *et al.* 1998; Syriänen *et al.* 1989; Armin *et al.* 2004). Nowadays it is obvious that a study of associations between periodontal infection and vascular atherogenesis requires the latest models and approaches because dental biofilms are polymicrobial infections and their interactive immunological action has not been clarified completely (Kebeschull *et al.* 2010).

It is known that classical risk factors such as hypertension, hyperlipidaemia, dyslipidaemia, diabetes mellitus, thrombophilia and atrial fibrillation do not fully explain the risk of cerebral stroke development. The presence of infection in these processes is being seen more and more and is associated with undergone infectious diseases. Frequent sources of infection are acute respiratory as well as urological and dental infections. When examining the time factor, some studies state that infection can complement classical risk factors, its highest intensity being observed within 3 days of an acute stroke. It is possible that the influence of the overall amount of bacteria is more of a limiting factor than the exposure of the organism to certain specific bacteria (Abolfazli *et al.* 2011; Palm *et al.* 2009).

For assessment of the association between chronic periodontitis and ischemic stroke, it is necessary to assess the existing inflammation state of the periodontitis. Periodontitis is known, as with any other chronic disease, to run in active and relatively quiet periods; i.e. in a sinusoid course. Some studies have accepted these facts and investigated the current inflammatory state of the chronic periodontitis in the 7-day period after stroke and have come to the conclusion that a periodontal inflammatory process is associated with an increased risk of the development of ischemic stroke (Abolfazli *et al.* 2011). Results of several studies quite clearly indicate that for further research it will be necessary to set clear and uniform criteria for diagnostics of periodontitis and the current state of inflammation in periodontal tissue and its severity, and then to associate all these facts with the incidence of cerebral stroke.

### Association of oral infection with atherothrombotic mechanisms

Oral bacteria (about 500 bacterial strains) colonise different structures of the oral cavity. They exist scattered in saliva in a planctonic form. If their ecological balance is destroyed for any reason, they can cause serious oral-plaque-induced diseases such as marginal

periodontitis and tooth caries. Many times in patients with chronic destructive periodontitis, transient bacteraemia, increased serum concentration of LP S-toxins of gram-negative anaerobes and different pro-inflammatory cells and cytokines have been detected. These cells and substances, along with the hugely increased pro-inflammatory status of the organism, can induce development of systemic atherothrombotic diseases. Some strains of streptococci and staphylococci as well as the main periodontal pathogen *P. gingivalis* stimulate thrombocytes *in vivo* as well as *in vitro* (Elkaim *et al.* 2008; McNicol *et al.* 2010).

*Porphyromonas gingivalis* as one of the dominant periodontopathological bacteria possesses a whole range of virulent factors involved in periodontal tissue destruction. One of the most important virulent factors are cysteine proteinases, for example the arginine-specific gingipains R (RgpB and HRgpA), which activate coagulation factors. These enzymes induce an increase of intra-cellular calcium in thrombocytes and raise their aggregation (Lourbakos *et al.* 2001).

#### Periodontitis stimulates several pro-atherogenic factors

Chronically destructive periodontitis induces several risk factors and atherosclerotic process inducing and accelerating mechanisms. Chief among these factors are:

- *Stimulation of CRP formation.* The long-term activity of specific bacteria in destructive periodontitis stimulate CRP formation and positively associate with the clinical picture of this disease. Increased CRP values have been detected in both diseases (Fentoglu *et al.* 2011; Saito *et al.* 2003).
- *Increased production of pro-inflammatory mediators stimulate hyperlipidaemia.* Chronic periodontitis stimulates formation of pro-inflammatory mediators, which activate production of de novo synthesized fatty acids in the liver and serum triglycerides and so contribute to increased hyperlipidaemia (Fentoglu *et al.* 2011; Feingold *et al.* 1992; Friedewald *et al.* 2009; Sang-Beon *et al.* 2012).
- *Induction of pro-atherogenic alteration of the lipid spectrum.* The LPS toxin of gram-negative bacteria negatively influences cholesterol metabolism and NF-kappa and decreases the expression of two important primary HDL receptors. Patients with periodontitis showed significantly decreased anti-atherogenic HDL potential and had increased serum concentrations of phospholipase A2 (Fentoglu *et al.* 2011; Feingold *et al.* 1992; Pussinen *et al.* 2004; Bulin *et al.* 2009).
- *Increase of oxidation stress of the organism and vessels.* Oxidation mechanisms play an important role in the development of atherosclerosis because LDL oxidation is one of the basic pro-atherogenic mechanisms in atherosclerosis development. Native LDLs penetrate in a sub-endothelial way where they are tolerated by means of scavenger receptors of macro-

phages from which so-called foam cells later develop (Ekumi *et al.* 2009; Tomofuji *et al.* 2009; Katz *et al.* 2001). Oxidised LDLs inhibit peroxide production, which is an important factor in vascular relaxation. When it is lacking, functional vasodilatation fails and peripheral resistance increases, while LDL oxidation, leukocyte migration, and adhesion and thrombocyte aggregation all decrease. In chronic periodontitis, changes of CO levels were observed. These can be genetically conditioned or due to the presence of *P. gingivalis* (Batista *et al.* 2002; Berdeli *et al.* 2006).

- *Increase of proteolytic activities in the organism and vessel wall.* Inflammatory periodontal processes activate certain serum metalloproteinase, which subsequently can participate in the destabilisation or even rupture of atherosclerotic lesion (Soder *et al.* 2009).

From the given factors it is clear that chronic inflammatory periodontal diseases have a significant inflammatory effect on the whole organism and can cause pro-atherogenic reactions in different regions, including the cerebral arteries.

### **TREATMENT PRINCIPLES AND DENTAL MANAGEMENT IN PATIENTS WITH A SUDDEN CEREBRAL ACCIDENT**

A basic requirement of the specific neurological treatment is to save the patient's life and keep their bodily functions going during and immediately after the stroke. A very important condition of post-infarction treatment and patient management is to prevent further infarction (Bergman 2011; Ali-Ali *et al.* 2011). The highest risk for further infarction is up to 33 per cent in patients in their first month after the first accident. This risk subsequently falls and in the first year represents about 14 per cent. The consequences of cerebral accidents are very variable. About 10 up to 20 per cent of patients must be treated in institutions, 15 to 30 per cent require specific care and approximately half of the surviving patients have minor limitation and consequences (Brandt *et al.* 2001; Bodnar *et al.* 2008; Suzuki *et al.* 2012). During dental treatment of patients after transient ischemic attack, we try to observe the following principles and procedures:

- a. Before the planned treatment we carefully inform the patient about symptoms, a detailed course, treatment, prognosis of the primary disease and its possible complications. It is necessary also to judge the consequences, complications and risk factors of stroke with regard to the planned treatment.
- b. During treatment it is necessary to check pains and blood pressure. During dental procedures, blood coagulation must be checked and anti-coagulation treatment interrupted at different time intervals depending on its type.

- c. Handicapped patients must be accompanied by a trained staff member that can provide them adequate information and is able to communicate with them. Treatment should be of short duration and should usually be done in the morning hours (Brandt *et al.* 2001; Bodnar *et al.* 2008).
  - d. When applying local anaesthesia, only minimum doses are recommended. The amount of vasoconstriction agent (noradrenalin, adrenalin) should be in a concentration of 1: 200,000 up to 1:100,000. We avoid application of vasoconstriction substances such as anaesthetics that cannot be easily controlled, as well as anaesthetics soaked in tissue (Bodnar *et al.* 2008).
  - e. Treatment of stroke patients is usually similar to dental treatment of patients with hypertension, where we have to keep certain principles and recommended procedure: to inform the patient about the course of treatment, painfulness of some procedures, monitoring of blood pressure in surgery and therapeutically formed norm tension. With blood pressure of over 200/115 it is necessary to induce a quick blood pressure drop with the assistance of an appropriate specialist. If pressure rises quickly, it is necessary to interrupt the procedure or to postpone it until later. Opinions on checking blood pressure in dental practice vary; the advocates of monitoring argue the necessity to use every occasion to detect hidden forms of hypertension, especially lighter forms. However opinions on the validity of measuring blood pressure in dental practice are relatively heterogeneous because this environment is stressful for many patients and can produce false positive results (Farkaš *et al.* 2012).
3. Present dental surgeries are equipped with a range of sophisticated and digitalised technology which enables effective cleaning of supragingival and subgingival spaces to eliminate pathogens and their systemic influence (PerioScan, Vector, Heal Ozon, Laser). DNA analyses of periodontal pathogens are also carried out in dental surgeries and enable effective antibiotic treatment. With laboratory techniques, it is possible to detect genetic polymorphisms IL-1: their positivity may lead to partially different management of a periodontological patient. These and many other techniques eliminate the catching areas for adhesion and colonisation of bacteria and significantly increase the number of patients treated in a non-invasive way. These methods and technology should be used more often and more extensively.
  4. Endodontic disciplines have qualitatively advanced with the progress of endodontic machines. The root canal cone can be processed with 6–9 per cent precision. Such enlargement of the canal enables the perfect rinsing of detritus and removal of larger amounts of pre-dentin and dentin from inside the root canals. Similarly it has contributed to simplification of treatment by means of apex locators and machining the root canals by digitalized devices and flexible NiTi tools, which significantly reduce their braking in the canal. They also enable treatment of crooked canals in molars.
  5. Peculiar attention has to be paid to subjects with severe destructive periodontitis in whom hypertension or some subclinical forms of atherosclerosis have been diagnosed. Early periodontal, cardiologic and anti-atherosclerotic treatment can subsequently lead to a decrease of infarctions in various sites.

## CONCLUSION

From the given facts, several conclusions can be drawn for dental surgery practice and patient management:

1. In subjects with progressive forms of periodontitis expressed by positive periodontal pocket depth indexes and bleeding, it is necessary to treat these clinical forms of disease by means of scaling, deep scaling, closed and open curettage, local and systemic medicine therapy in order to stabilize the disease to a point where the circulatory communication of the destroyed periodontium with the organism is decreased.
2. In patients with decay lesion with necrotic or gangrenous tooth pulp or osteolytic deposits in the alveolar bone, it is necessary to remove carefully the focuses and eradicate or reduce the amount of bacterial pathogens in this way in order to decrease the pro-inflammatory status of the organism by reducing formation of inflammatory cells and cytokines and so inhibit various atherogenic mechanisms.

At the end of this chapter we would like to state that dentists are fully aware of these problems and consistently try to remove focuses of infection in the oral cavity. This way they can eliminate inflammation, and diminish infectious agents and retentive sites of adhesion, colonisation and invasion. Internists, cardiologists, diabetologists, neurologists, gynaecologists and rheumatologists should also be called upon to deal with this problem in the same active way.

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