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Clinical experience for Porphyromonas gingivalis detection in the cerebrospinal fluid of patients with inflammatory diseases of the central nervous system and periodontitis

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Abstract

Background. Porphyromonas. gingivalis is one of the most aggressive periodontopathogens causing periodontitis. Present scientific evidence proves the possibility of the influence of P.gingivalis on the pathogenesis of inflammatory diseases of the central nervous system.

Objective. To verify frequency of P.gingivalis detection within the cerebrospinal fluid of patients affected by various types of CNS inflammatory diseases.

Material and Methods. Cerebrospinal fluid of 36 patients, aged 18 to 79 years, with various infectious diseases of the central nervous system was analyzed during two years of study. Real-time PCR technique was used for P.gingivalis detection.

Results: 13 patients out of 36 demonstrated the presence of P.gingivalis within cerebrospinal fluid. 4 of them were diagnosed with meningoencephalitis, 3 patients had fever of unknown origin, at that one of them had Parkinson's disease, 3 patients had acute disseminated unspecified demyelination, 1 had multiple sclerosis, 1 had unspecified cerebrovascular disease. 77% of the total number of patients in whom P.gingivalis was detected in the cerebrospinal fluid, also were diagnosed with periodontitis.

Conclusions: Based on the data obtained, it can be assumed that P.gingivalis plays a significant role in the pathogenesis of inflammatory diseases of the central nervous system. Sanitation of the oral cavity and timely treatment of periodontal diseases can significantly reduce the incidence of inflammatory diseases of the central nervous system.

Introduction

Currently, the influence of microflora vegetating in biofilms on the development and course of periodontitis has been scientifically proven. The occurrence and development of the disease depends on the presence of highly virulent microorganisms, the vital activity of which leads to the destruction of the epithelium and collagen of the gingival junction, and then to bone loss. A direct relationship has been established between the progression of generalized periodontitis and the level of bacterial contamination of the periodontal pocket by opportunistic and pathogenic microflora [1].

Nevertheless, several studies demonstrated presence of possible connections between the impact of P. gingivalis and course of non-odontogenic diseases, while other linked P.gingivalis with causal development of some somatic pathologies [2, 4, 5, 6].

The role of P.gingivalis in the development of cardiovascular diseases has been statistically reliably proven [2-4]. Moreover, P.gingivalis accelerates the development of atherosclerosis associated with indirect oxidative stress [5].

In Japan, a research was conducted studying the relationship of inflammatory diseases of the oral cavity, in particular caused by P.gingivalis, with the occurrence of infectious endocarditis. Published data suggest that patients with coronary heart disease (CHD) with infectious endocarditis (IE) have more severe periodontitis compared to patients without IE. Patients with IE had fewer remaining teeth, more pronounced bone resorption compared with patients without IE. These results suggest a possible relationship between the occurrence of IE and periodontitis [6].

Brazilian scientists recently published data regarding the condition of periodontitis tissue in patients from the intensive care unit (ICU) and patients without hospitalization (control group). It turned out that the prevalence of periodontitis was 39.7% among the control group and 59.0% among ICU patients. Inpatient intensive care units had a significantly higher incidence of cardiovascular diseases and periodontitis in history than in the control group. Bacterial indices of A. actinomycetemcomitans, T. denticola and P.gingivalis were

significantly higher in ICU patients with periodontitis than in the control group. Thus, patients in intensive care units had a higher prevalence of periodontitis and a worse periodontal condition (higher average plaque index, BOP, level of loss of clinical attachment ≥3 mm and probing depth from 4 to 6 mm [7].

American scientists published a work, where they characterized the course of periodontitis in patients with type 1 DM; it showed that the prevalence of cardiovascular diseases and systemic inflammatory markers (plasma interleukin-6 (IL-6) and serum titer of immunoglobulin G against P.gingivalis), are positively associated with the severity of periodontitis (P = 0.002 and 0.02, respectively). Antibody titers of P. gingivalis were positively and significantly correlated with cardiovascular diseases, serum IL-6, and highly sensitive C-reactive protein [8].

Also scientists have suggested that exposure to P.gingivalis antigens, commonly found in periodontal diseases, can enhance immune activation in hypertension and exacerbate increased BP, vascular inflammation, and vascular dysfunction. These results support the concept that Th1, during an immune response, induces bacterial antigens such as P.gingivalis and can increase sensitivity to low doses of angiotensin II, thus providing a mechanistic connection between chronic infection such as periodontitis and hypertension [9].

Modern scientific studies provide evidence that P.gingivalis may play a role in the pathogenesis of the central nervous system diseases, such as multiple sclerosis, causing demyelination and generating autoimmune processes [10, 11]. Considering prevalence of such diseases, their disabling effect and non-reversed outcomes, it is highly relevant to provide researches aimed at the investigation of the cerebrospinal fluid for the potential detection of periodontitis-associated microflora, which potentially may be affiliated with critical health deterioration of patient affected by primary neuroinflammatory disorders.

Objective

To verify frequency of P.gingivalis detection within the cerebrospinal fluid of patients affected by various types of CNS inflammatory diseases.

Materials and methods

Collection of CSF samples

Cerebrospinal fluid of 36 patients, aged 18 to 79 years, with various infectious diseases of the central nervous system was analyzed during two years of study.

Diagnostics of CSF was made in patients with various types of inflammatory diseases of the central nervous system (including demyelinating ones), especially in those patients where it was difficult to establish a diagnosis or diagnosing caused doubts.

The cerebrospinal fluid was taken during lumbar puncture in the inpatient departments of Kyiv City Clinical Hospital No. 4 as required by the protocol and in compliance with all aseptic and antiseptic rules [12]. The material was taken in disposable sterile, hermetically sealed tubes without filler. If the time from the moment of collection to delivery of the material was more than 2 hours, then it was stored in the refrigerator at a temperature of 6±2°C. The transport medium was not used. This method was used to exclude additional, even minimal dilution of the material during the study. In addition, when dividing the material immediately into Eppendorf tubes, cross-contamination of the material is excluded and further processing of the samples is facilitated. Each tube was marked accordingly and was accompanied by a label indicating the necessary data.

Real-time PCR technique

Real-time PCR technique was used for P.gingivalis detection. Using a real-time PCR system “Stomatophlor” quantitative assessment of the five major periodontopathogens (Tannerella forsythus (Bacteroides forsythus), Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Prevotella intermedia and Treponema denticola) of the red complex was performed [13]. This test system is used for microbiological assessment of the contents of the periodontal pocket in patients with periodontitis. It should be noted that the reagent kit includes: a mixture for PCR amplification specific for all bacteria, which allows determining the total bacterial mass; mixtures specific for microorganisms and a mixture for amplification of human genomic DNA (sampling control (SC)). SC is used to eliminate errors of the preanalytical stage. In addition, in the reagent kit, an internal control sample (IC) was added to the tubes with amplification mixtures to evaluate the efficiency of the polymerase chain reaction [13].

Collection of periodontal pockets’ material samples

The material from the periodontal pockets was taken from patients according to the generally accepted method and delivered to the laboratory using disposable sterile paper pins placed in 1.5 ml Eppendorf hermetically sealed plastic tubes [14, 15].

Preprocessing and processing of CSF samples and periodontal pockets’ material samples

At the stage of preprocessing the material from periodontal pockets, 100 µl of a sterile 0.9% sodium chloride solution (physiological solution) was added to each tube with paper pin using sterile disposable tips with an aerosol filter recommended for use in PCR laboratories. The tubes were left for 20 minutes at room temperature to extract the microbial mass into the solution. Every 5 minutes, the tubes were shaken for 3-5 seconds on a vortex to improve extraction. After extraction was completed, the tubes were centrifuged on a vortex at 1000 rpm for 30 seconds to precipitate droplets. After that, the paper pin was removed from the test tube with sterile forceps, carefully squeezing the excess liquid against the walls and disposed of in a container with disinfectant. 300 µl of lysis solution was added to the test tubes with the extract, and then nucleic acids were isolated according to the instructions for use of the reagent kit.

Also, at the preprocessing stage, an additional concentration of cerebrospinal fluid was performed. For this, 0.5 ml of cerebrospinal fluid was introduced into an Eppendorf test tube and centrifuged for 10 min at 13,000 rpm. Then the supernatant fluid was taken so that sediment with a volume of 100 µl remained. An additional 0.5 ml of cerebrospinal fluid was added to this sediment and centrifuged again for 10 min at 13,000 rpm. A 300 µl of sediment was taken from the supernatant fluid for further work, and nucleic acids were isolated according to the instructions for use of the reagent kit.

From the obtained nucleic acid preparations was performed amplification to detect pathogenic microorganisms of the oral cavity by real-time PCR.

After amplification was performed, according to the index of indicator cycle, the amount of each of the microorganisms was calculated programmatically (decimal concentration logarithm) [13, 14, 15]. The obtained values allow assess the presence of periodontopathogens in the cerebrospinal fluid.

Results

P.gingivalis was found in the CSF of 13 people, which is 36% of all studied. 4 of them were diagnosed with encephalomyelitis, 3 patients had fever of unknown origin, at that 1 patient had Parkinson's disease, 2 had acute disseminated demyelination, unspecified, 1 had multiple sclerosis, 1 had cerebrovascular disease, unspecified. In 1 patient P.gingivalis was detected after the consequences of inflammatory diseases of the central nervous system and in another patient with localized (focal) symptomatic epilepsy (Tab.1). All patients diagnosed with P.gingivalis were referred for consultation with a periodontist. 10 patients out of 13 were given a concomitant diagnosis, namely, chronic periodontitis of varying severity based on the PSR test. This accounted for 77% of the total number of patients in whom P.gingivalis was detected. In 3 patients, inflammation in the periodontal tissues at the level of gingivitis was determined. All patients underwent a microbiological test using the same system by real-time PCR, and P.gingivalis was detected in all 13 patients (100%).

Table 1. The amount Porphyromonas gingivalis received from cerebrospinal fluid

Patients, №	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Porphyromonas gingivalis, Lg	0,5	2,0	1,3	1,6	1,3	1,6	1,7	1,7	1,3	1,7	3,0	1,7	1,9	1,6	0,1	1,6
SC (sampling control), Lg	0,7	0,9	1,1	1,7	1,5	1,2	2,4	3,8	3,4	1,9	1,9	1,4	2,0	1,9	2,6	2,9

Clinical case

Presented clinical case demonstrates the importance of P.gingivalis detection within CSF of patient diagnosed with temporal-medial epilepsy, and use of targeted anti-P.gingivalis treatment.

Patient P., 62 years old, was admitted to the neurology department on 05/23/18 with complaints of headaches, generalized night cramps. As a result of the study, the patient was diagnosed with localized (focal) symptomatic epilepsy. Treatment for a month (Levitiracetam, Bioven mono) did not give the desired result. Headaches and cramps continued. For diagnostic purposes, a puncture was made, and cerebrospinal fluid was taken for examination. In the material by PCR method, P. givalivalis DNA was revealed, while no other abnormalities were detected (general cerebrospinal fluid analysis was unremarkable, cytosis of 2 cells, genetic markers of other infections were not detected). Signs of an inflammatory process in blood tests were also not detected. The patient was referred for consultation with a periodontist. She was diagnosed with chronic periodontitis of moderate severity, and a material from the periodontal pocket for microbiological examination was taken (Fig. 1). In the oral cavity, 4 periodontopathogens were detected in excess of the norm (Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythensis (Bacteroides forsythus), Treponema denticola), and also an excess of the total bacterial mass was noted. A periodontist performed the treatment, the patient was sanitized. For the treatment of neurological status, a combination of metronidazole (500 mg 3 times a day) and amoxicillin (1000 mg 2 times a day) for 14 days was included in the treatment regimen.

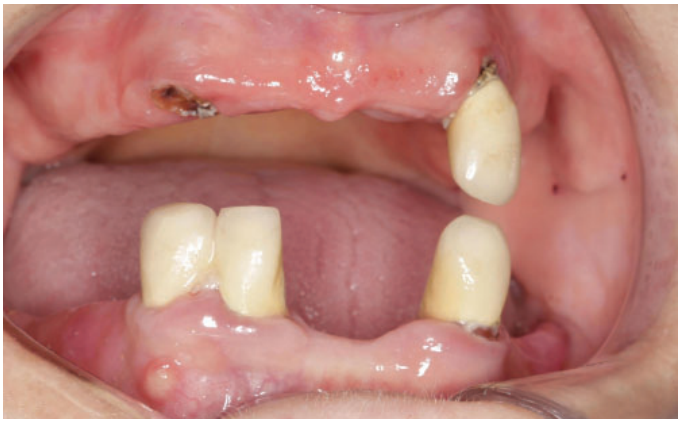

Figure 1. The state of the patient's oral cavity before treatment

After the treatment, the patient's condition improved. Neurological symptoms (headache, cramps) disappeared. In 6 months after treatment, a puncture and analysis of the cerebrospinal fluid was repeated, where P.gingivalis was not detected. In addition, the state of the oral cavity was stable, inflammation of periodontal tissues was not observed (Fig. 2a, b). The microflora in the oral cavity was normal. Exactly after the successful joint treatment by a neurologist and periodontist, we got an idea to study the cerebrospinal fluid of patients with various diseases of the central nervous system, whose diagnostics were difficult and standard treatment methods did not bring the results. Today, the hospital's doctors began to introduce a combination of amoxicillin and metronidazole into the treatment regimen, and we see that these drugs have positive results.

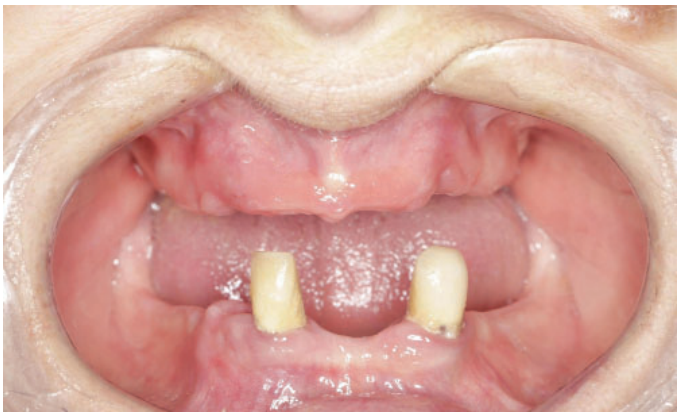

Figure 2a. The state of the oral cavity after treatment

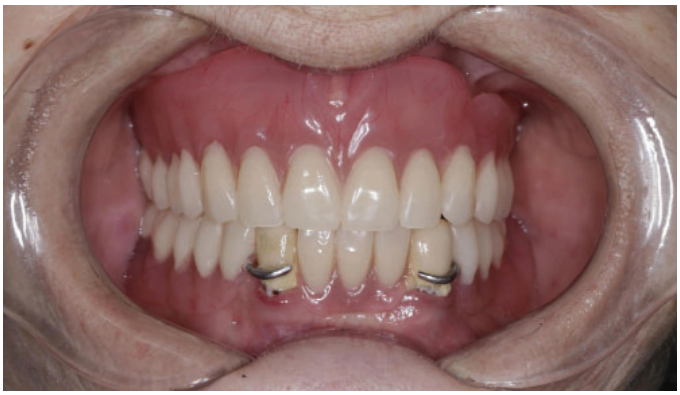

Figure 2b. The state of the oral cavity after treatment and rehabilitation

Discussion

To date, scientists from many countries are studying the relationship of P.gingivalis, as the most virulent microorganism in the oral cavity, with various diseases that at first glance are not related to dental infections. Especially such interrelations between P.gingivalis and CNS inflammatory diseases include important aspects for further investigations.

A study by Israeli scientists shows that oral infection of P.gingivalis increases the severity of autoimmune encephalitis (EAE) [10]. This may be due to a systemic pro-inflammatory response caused by P.gingivalis infection or imitation of antigen. This study provides evidence that periodontal infection may play a modifier role in inflammatory diseases of the central nervous system [10].

Previously Yoo et al. described a clinical case of brain abscess, anaerobic culture of which demonstrated presence of P. gingivalis [16]. Considering that previously patient presented with recurrent periodontitis, authors considered dental infection to be a cause of brain abscess [16]. Analogical case was also described by Iida et al., during which P. gingivalis was found in CSF of patient with severe brain abscess. Later Cruyssen et al. also reported a case of brain abscess in

which P. gingivalis was the only causative anaerobe microorganism due to the laboratory results obtained by spectrometry method [18].

Due to the results obtained by Sansores-España and colleagues, patients with Alzheimer's disease demonstrated more severe stage of periodontitis, higher levels of pro-inflammatory mediators and greater bacterial load compare to patients without Alzheimer's disease [19]. Chi et al. demonstrated that P. gingivalis may be linked to cognitive decline associated also with gut dysbiosis and neuroinflammation [20].

Recent systematic review demonstrated probability of P. gingivalis potential impact on the systematic inflammation, which in turn may be related with cerebrospinal fluid inflammation [21]. The latter effect may cause acceleration of Alzheimer's disease onset and its further progression. Nevertheless, such results should be interpreted with caution, since studies included into systematic review were characterized with pronounced heterogeneity of methodologies used during the research [21].

Singharo et al. mentioned that P.gingivalis effect over the brain may be associated with systematic cytokines and virulence factors encased within P. gingivalis outer membrane vesicles, which authors called "microbullets for sporadic Alzheimer's disease manifestation" [22]. Bregaint et al. pointed on such effect of P. gingivalis, as modulation of cellular homeostasis and amplification of inflammation markers, which could be linked with neurological diseases [23].

Olsen assumed that P. gingivalis may penetrate blood-brain barrier of elderly person even without Alzheimer's disease, because of its lowered stability and relatively higher permeability [24]. Even though P. gingivalis is not the only bacteria which potentially may enter the brain, it is characterized with possibility to provoke critically-significant dysbiosis effect even at very low concentration changes [24, 25]. That is why P. gingivalis should be one of the therapeutic targets for patients with Alzheimer's disease [25]. But what is more important doctor must realize that prophylaxis of P. gingivalis disseminations is the most effective prevention option regarding risk of Alzheimer's disease from the dental perspective [25].

The combination of the metronidazole and amoxicillin has been used in dentistry for many years, since drugs have a wide spectrum of action, penetrate the BBB and give positive results, affecting anaerobic bacteria, one of which is P.gingivalis [26]. That is why such combination was also used in the clinical case presented above. Also, Dominy et al suggested that gingipain inhibitors could be considered as treatment option for P. gingivalis brain colonization cases during neurodegeneration processes. Overall effect of gingipains was based on Aп1–42 production blockade, reduction of bacterial load, decrease of neuroinflammation and rescue of neurons in the hippocampus [27]. Animal-based model studiy approved two main effect of gingipains: 1) decrease of P. gingivalis DNA prevalence in brain; 2) reduction of neurotoxic effect caused by P. gingivalis [28]. That is why gingipains could potentially be considered at treatment option both for periodontitis and Alzheimer's disease.

Of course, further scientific research is needed to study in more detail the role of P.gingivalis in the etiology and pathogenesis of inflammatory diseases of the central nervous system, as well as the possibility of using a combination of metronidazole and amoxicillin in the treatment with the selection of the correct dose and treatment duration.

Conclusions

Based on our research, it can be assumed that P.gingivalis plays a significant role in the pathogenesis of inflammatory diseases of the central nervous system. This may be due to a systemic pro-inflammatory response caused by P.gingivalis infection. Sanitation of the oral cavity and timely treatment of periodontal diseases can significantly reduce the incidence of inflammatory diseases of the central nervous system. In the treatment regimen of these diseases, can be used drugs applied for periodontitis treatment, which have proven their long-term effectiveness. It is a combination of metronidazole and amoxicillin.

Conflict of interest

The authors don`t have any potential conflict of interests that may influence the decision to publish this article.

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Клінічний досвід виявлення Porphyromonas gingivalis у спинномозковій рідині хворих на пародонтит одночасно з запальними процесами центральної нервової системи

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Ключові слова:
Porphyromonas gingivalis, пародонтопатогени, пародонтит, запальні захворювання, центральна нервова система, спинномозкова рідина

Анотація

Вступ. Porphyromonas gingivalis є одним із найагресивніших пародонтопатогенів, що викликають пародонтит. Сучасні наукові дані підтверджують можливість впливу P.gingivalis на патогенез запальних захворювань центральної нервової системи.

Мета. Перевірити частоту виявлення P.gingivalis у спинномозковій рідині пацієнтів із різними видами запальних захворювань ЦНС.

Матеріали і методи. Впродовж двох років досліджено спинномозкову рідину 36 пацієнтів віком від 18 до 79 років з різними інфекційними захворюваннями центральної нервової системи. Для виявлення P.gingivalis використовували метод ПЛР у реальному часі.

Результати: у 13 пацієнтів із 36 досліджених виявлено наявність P.gingivalis у спинномозковій рідині. З них у 4 хворих діагностовано менінгоенцефаліт, у 3 хворих - гарячка невідомого генезу, при цьому в одного з них – хвороба Паркінсона, у 3 хворих – гостра дисемінована неуточнена демієлінізація, у 1 хворого – розсіяний склероз і у 1 хворого – неуточнена цереброваскулярна хвороба. У 77% від загальної кількості хворих, у яких виявлено P.gingivalis в спинномозковій рідині також був діагностований пародонтит.

Висновки. На основі отриманих даних можна припустити, що P.gingivalis відіграє значну роль у патогенезі запальних захворювань центральної нервової системи. Санація порожнини рота і своєчасне лікування захворювань пародонту дозволяє значно знизити захворюваність на запальні захворювання центральної нервової системи.

Конфлікт інтересів
Автори не мають потенційного конфлікту інтересів, який міг би вплинути на рішення про публікацію цієї статті..

Фінансування
Автори не отримували фінансової підтримки від жодної організації для проведення свого дослідження.

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