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GENETIC AND INFECTIOUS FACTORS PREDISPOSING TO PERIODONTITIS ON THE BACKGROUND OF OSTEOPENIA

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The purpose of this study was to examine the association of single nucleotide polymorphisms of TNFSF11, TNFRSF11B, SOST, ZNF385B and LRP5 genes involved in bone metabolism with the risk of periodontitis, as well as to assess the infection of the oral cavity with *Porphyromonas gingivalis* in the presence of periodontitis, osteopenia and periodontitis with osteopenia. The study included patients with periodontitis (13 patients), osteopenia (8 patients), periodontitis with osteopenia (11 patients) and a control group (23 patients). The A-allele of the rs6757845 G>A polymorphism of the ZNF385B gene increased the risk of periodontitis in the heterozygous state and in the dominant inheritance model. Differences between the study groups in the distribution of frequencies of genotypes and alleles of other polymorphisms were not statistically significant. The number of *Porphyromonas gingivalis* bacteria in gingival sulcus/periodontal pocket fluid samples of patients with osteopenia and periodontitis with osteopenia was significantly higher than in the control group and the group of patients with periodontitis.

Key words: osteopenia, oral health, polymorphism, genotyping, oral bacteria.

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ГЕНЕТИЧНІ ТА ІНФЕКЦІЙНІ ФАКТОРИ СХИЛЬНОСТІ ДО ПАРОДОНТИТУ НА ТЛІ ОСТЕОПЕНІЇ

Метою цього дослідження було вивчення асоціації однонуклеотидних поліморфізмів генів TNFSF11, TNFRSF11B, SOST, ZNF385B і LRP5, які беруть участь у метаболізмі кісткової тканини, з ризиком розвитку пародонтиту, а також оцінка інфікування ротової порожнини *Porphyromonas gingivalis* за наявності пародонтиту, остеопенії та пародонтиту на тлі остеопенії. У дослідження включено пацієнтів із пародонтитом (13 осіб), остеопенією (8 осіб), пародонтитом на тлі остеопенії (11 осіб) і контрольну групу (23 особи). А-алель поліморфізму rs6757845 G>A гена ZNF385B підвищував ризик пародонтиту в гетерозиготному стані та в домінантній моделі успадкування. Відмінності між досліджуваними групами за розподілом частот генотипів і алелів інших поліморфізмів не були статистично достовірними. Кількість бактерій *Porphyromonas gingivalis* у зразках рідини ясенної борозни/пародонтальних кишень пацієнтів з остеопенією і пародонтитом на тлі остеопенії вірогідно перевищувала аналогічний показник у контрольній групі та групі пацієнтів із пародонтитом.

Ключові слова: остеопенія, здоров'я порожнини рота, поліморфізм, генотипування, бактерії порожнини рота.

The work is a fragment of the research project "Correction of pathogenetic mechanisms of disorders of carbohydrate and lipid metabolism in the body and tissues of the oral cavity in patients depending on environmental and nutritional factors affecting carbohydrate and lipid metabolism", state registration No. 0118U006966.

Periodontitis is a bacterial microflora-induced chronic inflammatory lesion of the supporting structures of teeth and is characterized by progressive destruction of the entire periodontium, which includes both soft and hard tissues, i.e., gingiva, cementum, periodontal ligament, and alveolar bone. Periodontitis is caused by an uncontrolled inflammatory response to persistent colonization by pathogens, particularly Porphyromonas gingivalis, of the tooth-gingival margins and the gingival crevice [9]. Individual features of the inflammatory response are largely determined by genetic factors, such as polymorphisms of IL1A, IL1B, IL4, IL6, IL10, TNFA, FcγR, VDR, TLR2, TLR4, and MMP1 genes [2, 4,5, 10, 11, 13, 14]. The identification of novel inherited factors in periodontitis is of great clinical importance for its early recognition and expansion of therapeutic options.

The causes of periodontitis also include disorders associated with a decrease in bone mineral density. A moderate form of this disorder is osteopenia, an initial and often reversible decrease in bone mineral density due to an imbalance between bone resorption and bone formation, with resorption predominating. In Caucasian women at menopause, osteopenia is associated with interproximal alveolar bone loss and, to a lesser extent, with clinical loss of tooth attachments [8].

The purpose of the study was to search for association of specific single nucleotide polymorphisms with periodontitis and compare the presence of P. gingivalis in various patient groups.

Materials and methods. The study involved 55 patients aged 25–55 years. Among them were patients with periodontitis (n=13), osteopenia (n=8), periodontitis with osteopenia (n=11) and control group (n=23).

Dental examination was conducted in the dental office at the Department of Epidemiology and Prevention of Major Dental Diseases, Pediatric Dentistry and Orthodontics of the SE "The Institute of stomatology and maxilla-facial surgery National academy of medical sciences of Ukraine" (SE "ISMFS NAMS").

DNA from buccal epithelial cells was isolated using a Chelex method [15]. DNA concentration and purity were spectrophotometrically determined (Nanophotometr, Implen, Germany). To study the rs2277438 TNFSF11 – 438 A>G polymorphism, allele-specific three-primer PCR was used. Allelic variants of the polymorphisms rs2073617 TNFRSF11B 950C>T, rs865429 SOST 675C>T, rs6757845 ZNF385B G>A, and rs41494349 LRP5 266 A>G were evaluated using PCR-PDRF with primers from Metabion (Germany). Amplification products underwent restriction enzyme treatment. Results were visualized on a 2 % agarose gel. Microbiological samples from the oral cavity were taken with endodontic pins and stored in Eppendorf tubes. Bacterial DNA was isolated using the "DNA-EXPRESS" kit (NPF "Litech"), and P. gingivalis presence was determined on a CFX96 Touch "REAL TIME" amplifier (Bio-Rad, USA).

Statistical processing of the obtained results, including the test for deviation from the Hardy-Weinberg equilibrium (HWE) and the assessment of the association of genotypes and alleles with the risk of periodontitis by the Pearson $\chi 2$ method, was carried out using the DeFinetti genetic statistics program on the website of the Institute of Genetics (Munich, Germany). Associations were characterized by odds ratio (OR) with 95 % confidence interval and Pearson's $\chi 2$ test. Comparison of logarithmically transformed (log) number of *P. gingivalis* in different groups was performed by Mann-Whitney test using the MedCalc statistical software package (MedCalc Software Ltd, Belgium). The difference was considered to be statistically significant at $p<0.05$ [1].

Results of the study and their discussion. Genotyping of polymorphisms rs2073617 TNFRSF11B 950C>T, rs865429 SOST 675C>T, rs2277438 TNFSF11 – 438 A>G, rs6757845 ZNF385B G>A and rs41494349 LRP5 266 A>G in the group of patients with periodontitis (n=13) and in the control group (n=23) was performed. The genotype frequency distribution and its conformity to Hardy-Weinberg equilibrium (HWE), as well as the differences between groups in genotype and allele frequency distribution were analyzed in the studied groups. Only the AA genotype of the rs41494349 LRP5 266A>G polymorphism was detected in both groups, so this polymorphism was excluded from further analysis. For the other polymorphisms, the genotype distribution frequencies corresponded to those theoretically calculated for HWE both in the experiment and in the control ($p>0.05$, Table 1,2).

Table 1

Distribution and comparison of frequencies of genotypes and alleles of rs2277438 TNFSF11 –438 A>G and rs6757845 ZNF385B G>A polymorphisms in patient groups

Polymorphism	rs2073617 TNFRSF11B 950C>T					
Genotype, allele	CC	CT	TT	Alele C	Alele T	HWE p-value
Case, frequency	0.231	0.615	0.154	0.539	0.461	0.390
Control, frequency	0.304	0.348	0.348	0.478	0.522	0.146
Comparison of frequencies	T<>C	CT<>CC	CT+TT<>CC *DM*	TT<>CC+CT *RM*	–	–
OR (95 % CI)	0.786 (0.300–.060)	2.333(0.439–2.398)	1.458 (0.305–6.984)	0.583 (0.075–562)	–	–
$\chi 2$ p-value	0.623	0.315	0.635	0.605	–	–
Polymorphism	rs6757845 ZNF385B G>A					
Genotype, allele	GG	GA	AA	Alele G	Alele A	HWE p-value
Case, frequency	0.385	0.615	0.000	0.692	0.308	0.109
Control, frequency	0.783	0.174	0.043	0.870	0.130	0.263
Comparison of frequencies	A<>G	GA<>GG	GA+AA<>GG *DM*	AA<>GG+GA *RM*	–	–
OR (95 % CI)	2.963 (0.896–9.796)	200 (1.518–34.139)	5.760 (1.294–25.644)	1.121 (0.040–31.613)	–	–
$\chi 2$ p-value	0.067	0.009	0.016	0.600	–	–

Note. CI – confidence interval; DM – dominant model; RM – recessive model; HWE – Hardy-Weinberg equilibrium. Significant values of the odds ratio (95 % CI) and values of $p<0.05$ are highlighted in bold.

The distribution of genotypes and alleles of the ZNF385B rs6757845 G>A single nucleotide polymorphism of the ZNF385B gene was different between the studied groups. The frequency of the mutant A allele rs2073617 in the group of patients with periodontitis was higher than in the control group: 0.308 and 0.130, respectively. The A allele of the rs6757845 ZNF385B G>A polymorphism was associated with the risk of periodontitis in the heterozygous condition GA<>GG, OR=7.200 (95 % CI 1.518–34.139), $\chi 2$ significance p=0.009; and in the dominant pattern GA+AA<>GG, OR=5.760 (95 % CI 1.294–25.644), p=0.016.

The differences between the studied groups in the distribution of genotype and allele frequencies of the other polymorphisms were not statistically significant (Table 2).

Table 2

Distribution and comparison of frequencies of genotypes and alleles of rs2073617 TNFRSF11B 950C>T and rs865429 SOST 675C>T polymorphisms in patient groups

Polymorphism	rs2277438 TNFSF11 –438 A>G					
Genotype, allele	AA	AG	GG	Alele A	Alele G	HWE p-value
Case, frequency	0.000	0.308	0.692	0.154	0.846	0.512
Control, frequency	0.043	0.609	0.348	0.278	0.722	0.102
Comparison of frequencies		AG<>AA	AG+GG<>AA *DM*	GG<>AA+AG *RM*	–	–
OR (95 % CI)	2.933 (861–9.996)	0.931 (0.032–27.096)	1.800 (0.068–7.406)	3.353 (0.120–93.835)	–	–
$\chi 2$ p-value	0.077	0.595	0.445	0.303	–	–
Polymorphism	rs865429 SOST 675C>T					
Genotype, allele	CC	CT	TT	Alele C	Alele T	HWE p-value
Case, frequency	0.077	0.308	0.615	0.231	0.769	0.630
Control, frequency	0.087	0.522	0.391	0.348	0.652	0.472
Comparison of frequencies	T<>C	CT<>CC	CT+TT<>CC *DM*	TT<>CC+CT *RM*	–	–
OR (95 % CI)	1.778 (0.594–5.318)	0.667 (0.047–9.472)	1.143 (0.094–13.965)	1.778 (0.134–23.520)	–	–
$\chi 2$ p-value	0.300	0.763	0.916	0.659	–	–

Note. CI – confidence interval; DM – dominant model; RM – recessive model; HWE – Hardy-Weinberg equilibrium. Significant values of the odds ratio (95 % CI) and values of $p<0.05$ are highlighted in bold.

Quantification of P. gingivalis in gingival sulcus/parodontal pocket fluid samples of patients with periodontitis, osteopenia, periodontitis and osteopenia, and controls was also performed (Fig. 1).

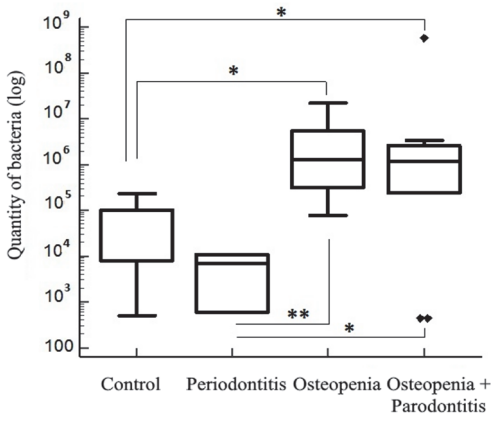

Fig.1. Quantitative distribution of Porphyromonas gingivalis in samples from individuals of the control group, patients with periodontitis, osteopenia and periodontitis on the background of osteopenia. Differences are significant at *$p<0.05$ and $p<0.01$.

Median values of bacterial counts in the control and periodontitis patient groups did not differ significantly: Mann-Whitney U-criterion=16, p=0.124. The number of bacteria in the samples of patients with osteopenia and periodontitis on the background of osteopenia significantly exceeded this indicator in the control group (p=0.012 and 0.013, respectively) and in the group of patients with osteopenia (p=0.002 and 0.033, respectively). Patients with osteopenia and patients with periodontitis on the background of osteopenia did not differ significantly in the number of P. gingivalis in the samples: p=0.316.

The contribution of the genetic component to the pathogenesis of such a multifactorial disease as periodontitis is estimated at 30–40 % of the total clade of all factors. In turn, genetic predisposition to periodontitis can be determined by numerous genetic polymorphisms, the total effect of which plays a more significant role in the variability of disease manifestations compared to individual gene effects [7]. We have studied the association of polymorphisms of genes involved in bone metabolism with the risk of periodontitis. The genes TNFRSF11B (Tumor necrosis factor receptor superfamily member 11B, known as OPG, osteoprotegerin) and TNFSF11 (Tumor necrosis factor ligand superfamily member 11, aka RANKL, Receptor activator of nuclear factor kappa-B ligand) are components of the TNFRSF11A/TNFSF11/TNFRSF11B axis, which plays an important role in maintaining the balance between the processes of bone resorption by osteoclasts and bone formation by osteoblasts, in the regulation of bone remodeling, osteoclast differentiation, and osteolysis. The genes LRP5 (encodes a transmembrane receptor of low-density lipoproteins, which is involved in Wnt/β-catenin signaling pathway) and SOST (sclerostin, an endogenous inhibitor of Wnt/β-catenin signaling pathway) are associated with changes in bone mineral density and fracture risk. Although the single-nucleotide polymorphisms of these genes analyzed by us were not associated with the risk of periodontitis, the influence of minor effects of TNFRSF11B, TNFSF11, and SOST polymorphisms in the pathogenesis of periodontitis cannot be excluded, which requires confirmation in the course of further studies. The polymorphism rs41494349 LRP5 266 A>G apparently is not common in the Ukrainian population, as only AA genotype was observed in patients of both study groups

[2]. Our study revealed a significant association of ZNF385B gene rs6757845 G>A polymorphism with periodontitis. The ZNF385B gene, also known as ZNF533, belongs to the zinc-finger gene family. Their protein products contain a small "zinc finger" structural motif that interacts with DNA, RNA, other proteins and molecules. ZNF genes encode transcription factors that regulate the expression of other genes. ZNF385B is hypothesized to be a suppressor of transcription. The ZNF385B rs6757845 G>A polymorphism is poorly studied; this polymorphism is known to be associated with the formation of nonsyndromic orofacial clefts in the Chinese population [4]. Our identified association of rs6757845 with periodontitis needs further experimental confirmation and study using a larger number of patients.

P. gingivalis, a gram-negative anaerobe with black pigmentation, is one of the main causative agents of periodontitis and is included in the so-called "red complex" of the main periodontal pathogens along with Tannerella forsythia and Treponema denticola [3, 6]. In our study, the amount of this pathogen in periodontal pockets of periodontitis patients in general did not differ significantly from that in gingival sulcus fluid samples of control group individuals, which can be explained by the small representativeness of the patient group. At the same time, we found a significant increase in the number of P. gingivalis in periodontitis patients on the background of osteopenia, as well as in patients with osteopenia. Indeed, osteopenia may be one of the factors aggravating the course of periodontitis, since the general decrease in bone mineral density as a result of impaired bone metabolism extends to the alveolar bones of the upper and lower jaw, which contributes to the pathogenesis of periodontitis.

At the same time, infection with P. gingivalis infection in the oral cavity may contribute not only to the development of periodontitis, but also osteopenia, and aggravate the course of periodontitis against the background of osteopenia, since it is known that lipopolysaccharides, lipids, metabolic products, and sonicated extracts of this pathogen can inhibit the differentiation and osteogenesis of osteoblasts, metabolic products and sonicated extracts of this pathogen can inhibit differentiation and osteogenesis of osteoblasts, as well as modulate RANKL and/or OPG in osteoblasts for indirect stimulation of osteoclastogenesis – bone tissue removal through dissolution of the mineral component and collagen destruction. It has been shown that P. gingivalis can invade osteoblasts and inhibit their maturation and mineralization in vitro. When P. gingivalis cells enter the bloodstream, they bind erythrocytes, move along vessels under their cover, which helps to avoid phagocytosis, and colonize surrounding tissues, taking part in the development of rheumatoid arthritis, Alzheimer's disease, atherosclerosis, and other systemic diseases. Oral infection with *P. gingivalis* not only causes local alveolar bone loss, but also enhances the decrease in articular bone mineral density in mice with arthritis. The increased content of P. gingivalis in the oral cavity in osteopenia and periodontitis on the background of osteopenia revealed by us indicates the relationship between these diseases, as well as the role of P. gingivalis in local (periodontitis) and general (osteopenia) processes of bone tissue metabolism disorders [12].

Conclusions

1. The A allele of the single nucleotide polymorphism rs6757845 G>A of the ZNF385B gene is a risk factor for periodontitis.

2. Colonization of the oral cavity by the periodontopathogen P. gingivalis is associated with osteopenia, as well as periodontitis on the background of osteopenia.

3. Polymorphisms rs2073617 950C>T of TNFRSF11B gene, rs865429 675C>T of SOST gene, rs2277438 –438 A>G of TNFSF11 gene and rs41494349 266A>G of LRP5 gene are not associated with the risk of periodontitis development, but it is not excluded that possible minor effects of these polymorphisms were not sufficiently expressed in the studied sample of patients.

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OCCURRENCE AND CLINICAL EVOLUTION OF NEUROPATHIC DYSESTHETIC PAIN IN MULTIPLE SCLEROSIS (2-YEAR PROSPECTIVE STUDY)

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The occurrence and evolution of neuropathic dysesthetic pain in patients with multiple sclerosis during a 2-year observation period was studied. 241 patients were included in the study. Dysesthetic pain was diagnosed using the PainDETECT questionnaire. Patients with newly detected (recurrent) dysesthetic pain were examined at the beginning of the study, after 1, 3 and 6 months depending on the duration of the pain. Over a 2-year period, the cumulative risk of dysesthetic pain was 15.6 % (11.4 %–21.0 %), and the cumulative risk of recurrence was 8.8 % (3.0 %–23.0 %). The first detected (recurrent) dysesthesia lasted more than 3 months in two-thirds of cases. The first detected (recurrent) dysesthesia was mainly localized in the lower back and lower limbs. Patients described dysesthesia both at the time of its occurrence and later, indicating more than 2 descriptors (most often "burning", "freezing" and "tingling"). The chronicity of dysesthetic pain was associated with the expansion of pain areas, with the transformation of the pain pattern (from pain attacks to constant pain), with a decrease in pain intensity.

Key words: multiple sclerosis, neuropathic dysesthetic pain, occurrence, clinical evolution.

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ВИНИКНЕННЯ ТА КЛІНІЧНА ЕВОЛЮЦІЯ НЕЙРОПАТИЧНОГО ДИЗЕСТЕТИЧНОГО БОЛЮ ПРИ РОЗСІЯНОМУ СКЛЕРОЗІ (2-РІЧНЕ ПРОСПЕКТИВНЕ ДОСЛІДЖЕННЯ)

Вивчено виникнення та еволюцію нейропатичного дизестезичного болю у пацієнтів з розсіяним склерозом протягом 2-річного періоду спостереження. Залучено до дослідження 241 пацієнт. Дизестезичний біль діагностувався за опитувальником PainDETECT. Пацієнтів із вперше виявленим (рецидивним) дизестезичним болем обстежували на початку дослідження, через 1, 3 та 6 місяців залежно від тривалості болю. За 2-річний період кумулятивний ризик виникнення дизестезичного болю становив 15,6 % (11,4 %–21,0 %), а кумулятивний ризик рецидиву – 8,8 % (3,0 %–23,0 %). Вперше виявлений (рецидивний) дизестезичний у двох третинах випадків тривав більше 3 місяців. Вперше виявлений (рецидивний) дизестезичний переважно локалізувався в нижній частині спини та нижніх кінцівках. Пацієнти описували дизестезичний як на момент його виникнення, так і пізніше, вказуючи більше 2 дескрипторів (найчастіше «печіння», «морозіння» та «поколювання»). Хронізація дизестезичного болю асоціювалася з розширенням ділянок болю, з трансформацією больового паттерну (від больових нападів до постійного болю), зі зниженням інтенсивності болю.

Ключові слова: розсіяний склероз, нейропатичний дизестезичний біль, виникнення, клінічна еволюція.

The study is a fragment of the research project "Optimization of diagnosis, prognosis and prevention of neuropsychological disorders in organic diseases of the nervous system", state registration No. 0120U104165.

Clinical neurologists and neuroscientists have focused on dysfunctions in neurological diseases in the last 10 years that go beyond physical disability [2]. Multiple sclerosis (MS) besides well-known functional disabilities, has a wide variety of other disorders, including pain syndromes [1]. Classifications of pain in MS distinguish between neuropathic pain (NP), nociceptive pain and mixed pain [13]. NP is most directly related to the pathology of MS and its prevalence has been estimated to be 29 % in a meta-