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The role of interleukin-10 gene polymorphism (rs 1800872) in the course of herpes zoster in adults

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Aim. The aim of the work was to determine the role of polymorphism of the interleukin-10 gene (rs 1800872) in the course of herpes zoster in adults.

Materials and methods. 50 adult patients with herpes zoster were included into the study. The clinical course of the disease and development of the certain nature of complications were analyzed depending on the genetic polymorphism of the interleukin-10 gene. Statistical data processing was performed with using the formed patient database in the program STATISTICA for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Results. It was established that genotype TT of the IL-10 gene (rs 1800872) was recorded in 30 (60.0 %) patients with herpes zoster versus 14 (35.0 %) healthy people from the control group (P = 0.02), which confirmed the significance of the gene polymorphism IL-10 in reactivation of the varicella zoster virus and the manifestation of shingles. Analysis of the polymorphism of the IL-10 gene depending on the clinical form and the severity of shingle showed that genotype TT was significantly more frequently recorded in patients with severe course disease (86.7 % vs. 48.6 %, P = 0.01), however, did not influenced on the formation of certain clinical forms of the disease (P > 0.05). In patients with herpes zoster polymorphism of the IL-10 gene (rs 1800872) influenced the severity of the course of the disease, namely, the TT genotype was associated with a severe course of the disease (P = 0.01) and the development of neurological complications (P = 0.03), which were represented by meningitis (6), Ramsey-Hunt syndrome (3) and the subsequent formation of postherpetic neuralgia (3), as well as of ophthalmic nature (P = 0.0001), which were represented by herpetic blepharoconjunctivitis (16), keratouveitis (3), iridocyclitis (1), subconjunctival hemorrhages (1). Unlike the TT genotype, genotype TG of the IL-10 gene (rs 1800872) was associated with the development of complications with the addition of secondary bacterial microflora (χ^2 = 4.5, P = 0.03), the incidence of which did not depend on the severity of herpes zoster (P > 0.05).

Conclusions. In patients with herpes zoster, the TT-genotype of the IL-10 gene (rs 1800872) was associated with reactivation of the varicella zoster virus and development of a severe disease course, with formation of neurological (χ^2 = 4.75, P = 0.03) and ophthalmic (χ^2 = 14.75, P = 0.0001) complications. The TG genotype of the IL-10 gene (rs 1800872) is associated with the development of complications associated with the addition of secondary bacterial microflora (χ^2 = 4.5, P = 0.03).

Key words:
herpes zoster, interleukin-10, gene polymorphism.

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Роль поліморфізму гена інтерлейкіну-10 (rs 1800872) в перебігу оперізувального герпесу в дорослих

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Мета роботи – визначити роль поліморфізму гена інтерлейкіну-10 (rs 1800872) в перебігу оперізувального герпесу в дорослих.

Матеріали та методи. У дослідження залучили 50 дорослих хворих на оперізувальний герпес. Проаналізували клінічний перебіг захворювання та розвиток певного характеру ускладнень залежно від наявності поліморфізму гена інтерлейкіну-10. Статистичне опрацювання даних здійснили з використанням сформованої бази даних пацієнтів у програмі Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Результати. Встановили, що генотип ТТ гена ІЛ-10 (rs 1800872) зареєстрували у 30 (60,0 %) хворих на оперізувальний герпес проти 14 (35,0 %) здорових осіб контрольної групи (p = 0,02), що підтверджувало значення поліморфізму гена ІЛ-10 у реактивації Varicella Zoster Virus і маніфестації оперізувального герпесу. Аналіз поліморфізму гена ІЛ-10 (rs 1800872) залежно від клінічної форми та ступеня тяжкості оперізувального герпесу показав, що ТТ генотип вірогідно частіше реєстрували у хворих із тяжким перебігом захворювання (86,7 % проти 48,6 %, p = 0,01), проте не впливав на формування певних клінічних форм захворювання (p > 0,05). У хворих на оперізувальний герпес поліморфізм гена ІЛ-10 (rs 1800872) впливав на тяжкість перебігу захворювання: генотип ТТ асоціювався з тяжким перебігом захворювання (p = 0,01) і розвитком ускладнень неврологічного характеру (p = 0,03), що були представлені менінгітом (6), синдромом Рамсея-Ханта (3) та наступним формуванням постгерпетичної невралгії (3), а також офтальмологічного характеру (p = 0,0001), які були представлені герпетичним блефарокон'юнктивітом (16), кератоувеїтом (3), іридоциклітом (1), субкон'юнктивальним крововиливом (1). На відміну від генотипу ТТ, генотип ТG гена ІЛ-10 (rs 1800872) мав асоціацію з розвитком ускладнень, що пов'язані з приєднанням вторинної бактеріальної мікрофлори (χ^2 = 4,5, p = 0,03), частота розвитку яких не залежала від тяжкості перебігу оперізувального герпесу (p > 0,05).

Висновки. У хворих на оперізувальний герпес генотип ТТ гена ІЛ-10 (rs 1800872) асоціюється з реактивацією Varicella Zoster Virus і розвитком тяжкого перебігу захворювання з формуванням ускладнень неврологічного (χ^2 = 4,75, p = 0,03) та офтальмологічного (χ^2 = 14,75, p = 0,0001) характеру. Генотип ТG гена ІЛ-10 (rs 1800872) асоціюється з розвитком ускладнень, котрі пов'язані з приєднанням вторинної бактеріальної мікрофлори (χ^2 = 4,5, p = 0,03).

Ключові слова:
оперізувальний герпес, інтерлейкін-10, поліморфізм гена.

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Ключевые слова: опоясывающий герпес, интерлейкин-10, полиморфизм гена.

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Роль полиморфизма гена интерлейкина-10 (rs 1800872) в течении опоясывающего герпеса у взрослых

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Цель работы – определить роль полиморфизма гена интерлейкина-10 (rs 1800872) в течении опоясывающего герпеса у взрослых.

Материалы и методы. В исследование включены 50 взрослых больных опоясывающим герпесом. Проведен анализ клинического течения заболевания и развития определенного характера осложнений в зависимости от наличия полиморфизма гена интерлейкина-10. Статистическую обработку данных осуществляли с использованием базы данных пациентов в программе «STATISTICA for Windows 13» (StatSoft Inc., № JPZ804I382130ARCN10-J).

Результаты. Установлено, что генотип ТТ гена ИЛ-10 (rs 1800872) зарегистрирован у 30 (60,0 %) больных опоясывающим герпесом против 14 (35,0 %) здоровых лиц контрольной группы (p = 0,02), что подтверждало значение полиморфизма гена ИЛ-10 в реактивации вируса варицелла зостер и манифестации опоясывающего герпеса. Анализ полиморфизма гена ИЛ-10 (rs 1800872) в зависимости от клинической формы и степени тяжести опоясывающего герпеса показал, что генотип ТТ достоверно чаще регистрировали у больных с тяжелым течением заболевания (86,7 % против 48,6 %, p = 0,01), однако не влиял на формирование определенных клинических форм заболевания (p > 0,05). У больных опоясывающим герпесом полиморфизм гена ИЛ-10 (rs 1800872) влиял на тяжесть течения заболевания, а именно генотип ТТ ассоциировался с тяжелым течением заболевания (p = 0,01) и развитием осложнений неврологического характера (p = 0,03), которые были представлены менингитом (6), синдромом Рамсея–Ханта (3) и последующим формированием постгерпетической невралгии (3), а также офтальмологического характера (p = 0,0001), которые были представлены герпетическим блефароконъюнктивитом (16), кератоувеитом (3), иридоциклитом (1), субконъюнктивальным кровоизлиянием (1). В отличие от генотипа ТТ, генотип TG гена ИЛ-10 (rs 1800872) имел ассоциацию с развитием осложнений, связанных с присоединением вторичной бактериальной микрофлоры (χ^2 = 4,5, p = 0,03), частота развития которых не зависела от тяжести течения опоясывающего герпеса (p > 0,05).

Выводы. У больных опоясывающим герпесом генотип ТТ гена ИЛ-10 (rs 1800872) ассоциируется с реактивацией вируса варицелла зостер и развитием тяжелого течения заболевания, с формированием осложнений неврологического (χ^2 = 4,75, p = 0,03) и офтальмологического (χ^2 = 14,75, p = 0,0001) характера. Генотип TG гена ИЛ-10 (rs 1800872) ассоциируется с развитием осложнений, связанных с присоединением вторичной бактериальной микрофлоры (χ^2 = 4,5, p = 0,03).

Herpes zoster is an infection caused by reactivation of latent varicella zoster virus, which applies to herpes virus of the 3rd type. It is believed that every third person during his life is ill with herpes zoster. Each year in Europe and the United States there are more than 1 million new cases of shingles, which are 4–5 cases per 1000 population [1]. In Ukraine, official statistics indicate that the incidence of this disease is 12–15 cases per 100 000 population. Mortality from herpes zoster worldwide ranges from 0.017 to 0.465 cases per 100 000 population annually [2].

It is known that incidence and severity of herpes zoster are directly dependent on age of the patients, which is explained by a decrease in the activity of cellular immunity in the elderly [3]. According to the meta-analysis, female sex, the presence of concomitant pathology are risk factor for the development of herpes zoster [4]. The results of retrospective studies showed us that risk factors also include an aggravating family history, namely the presence of cases of shingles in relatives [5]. However, in recent years, the topicality of this disease is due to a rapid increase of the incidence rate among young and middle-aged people [6].

Today, special attention is paid to study of immunopathogenesis of herpes zoster. According to some authors [7] reported, the nature of the course of herpes zoster primarily depends on the immunological reactivity of early T-cell immunity, and much less depends on antibody production. The severe course of the disease is associated with a reduced T-cell response to the virus and high viral load in the human body [8]. However, current research suggests the dependence of the immune response on the polymorphism of genes, encoding cytokines, which are mediators of intercellular interactions [9]. The study of genes encoding the activity of cytokines is important in predicting the onset of the disease, severity of its course, and also for individualization of therapy [10]. In our opinion, it is expedient to determine the role of polymorphism of the IL-10 gene, which is the main inhibitor of inflammation and cytokine cascade, in patients with herpes zoster [9,11]. IL-10 is synthesized on the surface of many cells and suppresses effectors function of macrophages, T-cells, natural killers, neutrophils; co-stimulates the thymocytes proliferation and ripening, chemotaxis [9]; enhances synthesis of mast cells, B-cells proliferation and secretion of immunoglobulins; weakens the effect of angiotensin II and restores vascular endothelium [11]. At present the role of polymorphism of cytokine genes in the course of herpes virus infections is intensively studied, in particular an attempt is made to figure out the role of the IL-10 gene polymorphism in resistance to the most common herpesviruses [12,13]. The foregoing determined the direction of our study.

Aim

To determine the role of polymorphism of the interleukin-10 gene (rs 1800872) in the course of herpes zoster in adults.

Materials and methods

This study included 50 adult patients who were examined and treated at the Department "Neuroinfection" of the communal institution "Zaporizhzhia Regional Clinical Infectious Disease Hospital" of Zaporizhzhia Regional Council. The age of the patients ranged from 27 to 85 years and made up 66.5 [55.0; 77.0] years. Among the hospitalized patients,

there were 19 (38.0 %) men and 31 (62.0 %) women. For the analysis of the obtained data, the patients were divided into groups depending on the severity of herpes zoster. The severity of shingles was determined based on the severity symptoms of intoxication, the duration and abundance of rash, the presence or absence of complications [14]. The moderate course of the disease was registered in 35 (70 %) patients, severe – in 15 (30 %) patients. All the patients had a negative blood test for antibodies to the human immunodeficiency virus. All the patients were included into the study randomly basis and by informed consent. The control group consisted of 40 healthy individuals who hadn't been sick of herpes zoster before. The age of persons of the control group ranged from 35 to 87 years, made up 64.5 [52.5; 73.5] years and weren't statistically different from the age of the examined patients (P > 0.05).

On the basis of the clinical laboratory of the Zaporizhzhia Regional Clinical Infectious Disease Hospital for all the patients traditional laboratory (general blood and urine analysis, liver tests, coagulogram, proteinogram) and instrumental (electrocardiograhy, chest X-ray examination) tests were performed. In the presence of clinical evidence, lumbar puncture was performed with a study of liquor for the diagnosis of meningitis.

Special investigations were carried out on the basis of the Department of Molecular Genetic Studies of the Training and Laboratory Center of the ZSMU (headed by prof. O. M. Kamyshny). Determination of the IL-10 gene (rs1800872) polymorphism was performed using samples of total DNA isolated from the whole venous blood by the standard method using a set of DNA-EXPRESS-BLOOD-PLUS reagents (LitTech, Russian Federation). The molecular genetic study was performed by polymerase chain reaction in real-time according to the manufacturer's instructions (Applied Biosystems, USA). The genotype was determined using the CFX-96 Touch Real-Time polymerase chain reaction product detection system (BIO-RAD Laboratories, Inc., USA) using sets of NP-512-100 (RU).

Statistical data processing was performed in Statistica for Windows 13 (StatSoft Inc., №JPZ804I382130ARCN10-J) by the formed patient database. To assess the significance of the differences between the quantitative features in the independent groups, the Mann-Whitney criterion was used, and the quality method χ^2 was used between qualitative features. Relatively significant differences were considered at P < 0.05. The odds ratio (OR) was calculated using the formula: OR = ad / bc, where "a" is the frequency of a particular allele in the group of patients with herpes zoster, "b" is the frequency of a particular allele in the comparison group, "c" and "d" are the total frequency of other alleles in the study and comparison groups, respectively. The boundaries of 95 % confidence interval (CI) for OR were calculated using the Woolf method [15].

Results

According to the results of our study, it was found that genotype TT gene IL-10 (rs 1800872) was registered in 30 (60.0 %) patients with herpes zoster, against 14 (35.0 %) healthy people in the control group (χ^2 = 5.56, P = 0.02), which confirmed the significance of IL-10 gene polymorphism in the reactivation of the varicela zoster virus and manifestation of shingles (*Table 1*).

The analysis of the dependence of clinical course and severity of herpes zoster from the polymorphism of the IL-10 gene (rs 1800872) showed that genotype TT was significantly more commonly registered in patients with severe course shingles, whereas in patients with moderate course genotype TG (χ^2 = 6.35, P = 0.01) was detected 3.85 times more often (*Table 1*). The additive inheritance model made it possible to confirm association of the presence genotype TT of gene IL-10 (rs 1800872) with high chances of developing severe course of herpes zoster (0.867 vs. 0.133, χ^2 = 6.35, OR = 6.88 95 % CI = 1.35–35.11)

To determine genetic factors that have a statistically significant effect on the development of certain clinical forms of herpes zoster and complications various genesis, we have used the additive inheritance model using the criterion χ^2. Analysis of the role of IL-10 gene (rs 1800872) polymorphism in the formation of various clinical forms of shingles in adults did not reveal statistically significant differences (P > 0.05). Localized forms or disseminated and generalized forms were registered at the same frequency in patients with different genotypes. In addition, when analyzing various localization of lesions in localized forms of herpes zoster, no differences were found in the presence of certain genotypes of the IL-10 gene (rs 1800872). However, it has been established that polymorphism of the IL-10 gene (rs 1800872) had influence on the severity of herpes zoster in adults, namely, genotype TT was associated with a severe course of the disease (0.867 vs. 0.468, χ^2 = 6.35, P = 0.01, OR = 6.88 95 % CI = 1.35–35.11) and development of neurological complications (0.857 vs. 0.4, χ^2 = 4.75, P = 0.03, OR = 9.0 95 % CI = 0.96–84.5), which were represented by meningitis (6), Ramsey-Hunt's syndrome (3) and subsequent formation of postherpetic neuralgia (3), and also ophthalmic (0.762 vs. 0.125, χ^2 = 14.75, P = 0.0001, OR = 22.4 95 % CI = 3.74–134.15) complications, which were represented by herpetic blepharoconjunctivitis (16), keratouveitis (3), iridocyclitis (1), subconjunctival hemorrhage (1) (*Table 2*).

Unlike the genotype TT, genotype TG of the IL-10 gene (rs 1800872) was associated with development of complications such as addition of secondary bacterial microflora (0.800 vs. 0.407, χ^2 = 4.5, P = 0.03, OR = 5.82 95 % CI = 1.03–32.79) (*Table 2*). It should be noted that the incidence of complications associated with the addition of secondary bacterial microflora didn't depend on the se-

Table 1. Comparison of the frequency of registration of polymorphism of the gene IL-10 (rs 1800872) in patients with herpes zoster, depending on the severity of the disease, abs (%)

Indicator	Control group (n = 40)	Patients with herpes zoster (n = 50)	Patients with herpes zoster	
			moderate course (n = 35)	severe course (n = 15)
Genotype TT	14 (35.0 %)	30 (60.0 %) *	17 (48.6 %)	13 (86.7 %) * **
Genotype TG	26 (65.0 %)	20 (40.0 %)	18 (51.4 %)	2 (13.3 %) * **

*: the difference is significant, compared with healthy people (P < 0.05); **: compared with patients with moderate course (P < 0.05).

Table 2. Correlation matrix of dependence of development complications of shingles with polymorphism of gene IL-10 (rs 1800872)

Indicator	Genotype TT	Genotype TG	Coefficient χ^2, P
Neurological (n = 7)	6 (85.7 %)	1 (14.3 %)	4.75, P = 0.03
Postherpetic neuralgia (n = 3)	3 (100 %)	0	3.45, P = 0.06
Ophthalmic (n = 21)	16 (76.2 %)	5 (23.8 %)	14.75, P = 0.0001
Visceral (hepatitis) (n = 10)	6 (60.0 %)	4 (40.0 %)	0.71, P = 0.4
Severe course (n = 15)	13 (86.7 %)	2 (13.3 %)	6.35, P = 0.01
Relapsing course (n = 4)	2 (50.0 %)	2(50.0 %)	0.18, p = 0.67
Clinical forms, in particular:			
localized (n = 42)	25 (50.0 %)	17 (34.0 %)	0.02, P = 0.87
generalized and disseminated (n = 8)	5 (10.0 %)	3 (6.0 %)	
Localization of lesion in localized forms (n = 42):			
trigeminal nerve (n = 33)	20 (47.6 %)	13 (30.9 %)	0.07, P = 0.78
paravertebral ganglia (n = 9)	5 (11.9 %)	4 (9.6 %)	
Secondary bacterial infection (n = 10)	2 (20.0 %)	8 (80.0 %)	4.5, P = 0.03

verity of herpes zoster (P > 0.05). These complications developed in 8 (22.8 %) patients with moderate and in 2 (13.3 %) patients with severe course of shingles.

Discussion

It is known that dominant role in controlling dissemination and generalization of varicella zoster virus belongs to the cellular immunity of Th1-type [8,16,17]. Recently, special attention has been paid to study the role of IL-10 in the course of this infection. IL-10 is the main cytokine, which limits inflammatory processes, protects endothelium of vessels by reducing the effect of angiotensin II and restoring the activity of nitric oxide synthase which is inhibited by inducers of endothelial dysfunction [9,18], also it has an analgesic function [19]. It is determined that increase level of IL-10 is important for induction of immunity, which finally influences the frequency of relapses and severity course of the disease caused by varicella zoster virus [15,20,21]. With appearance of molecular genetic research which allows us to determine the polymorphism of the genes of interleukins, there was an opportunity to deepen the knowledge about the immunopathogenesis of herpes zoster. According to the results of our research, it has been proved that the genotype TT of the gene IL-10 (rs 1800872) influences the reactivation of the varicella zoster virus and manifestation of herpes zoster, which confirms its detection more often (P = 0.02) in patients with herpes zoster (60.0 %), compared with healthy people (35.0 %). The results of our study overlap with the results of other researchers [22], which have proven the special role of the haplotype ATA IL-10, presence of which leads to insufficient production of IL-10 and causes reactivation of the virus. At the same time, the other study [23] demonstrated that the increased risk of manifestation of shingles is associated with the carrier of the haplotype GCC, allele 1082, IL-10. The connection of the genetic polymorphism of the main complex of histocompatibility HLA (Complex 5) with the risk of development of herpes zoster is also discussed [24].

For today herpes zoster is a fairly widespread disease among immunocompetent people. Shingles can manifest with various clinical forms and possibility to development severe complications, primarily nervous system and organ of vision [25,26]. Recently, in addition to meningitis and meningoencephalitis, Ramsey–Hunt syndrome, namely a cervical node ganglionitis, has often begun to be diagnosed, development of which can lead to paralysis of facial muscles and reduced hearing abruption [27]. The development of ophthalmic herpes, in which a complete loss of vision is possible due to lesion of the optic nerve and its atrophy, deserves particular attention [28]. No less widespread complication of shingles is postherpetic neuralgia, which can persist for several months after regression of rash, and often leads to a reduction in ability, and in some cases, to a person's disability [29]. In our study the association of the genotype TT gene IL-10 with a high risk development of severe course of herpes zoster, with the complications of neurological and ophthalmic character has been proved. In the modern literature, available to us, we did not find researches on studying the role of the polymorphism of IL-10 gene in the formation of certain complications of herpes zoster. At the same time, there are studies that demonstrate the role of quantitative content of this cytokine in the severity course of the disease. In patients with a moderate course of herpes zoster, the authors [7,21] found an increase in blood levels of IL-10, which was treated as an adequate immunological response to the virus, with ability to reconvalescence without development of different complications. However, in severe course of shingles there was an insufficient immunological reactivity of the organism, which was characterized by a constant level of IL-10 [8,17]. All of this scientific researches has a definite pathogenetic explanation, namely it is known that in damage of brain cells, neurogliocytes produce IL-10, which increases the vitality of brain cells [16,25].

In modern literature there are solitary scientific researches which concern to determining the role of cytokines in the formation of bacterial complications in infected of varicela zoster virus. Thus, the study [8] has shown that interleukin-6 and interferon-γ can be used as early markers for the identification of patients with a high risk of developing bacterial skin complications. The data obtained in our study showed association of the TG gene IL-10 (rs 1800872) carrier with a high risk development of complications related the addition of secondary bacterial microflora (OR = 5.82 95 % CI = 1.03–32.79).

Conclusions

1. The genotype TT of the gene IL-10 (rs 1800872) is associated with reactivation of the varicella zoster virus and manifestation of herpes zoster.

2. The genotype TT of the gene IL-10 (rs 1800872) is associated with severe (χ^2 = 6.35, P = 0.01) course of

shingles, development of neurological (χ^2 = 4.75, P = 0.03) and ophthalmologic (χ^2 = 14,75, P = 0,0001) complications.

3. In patients with herpes zoster, genotype TG of the gene IL-10 (rs 1800872) is associated with the development of complications related to the addition of secondary bacterial microflora (χ^2 = 4,5, P = 0,03).

Prospects for further research. In our opinion, the promising direction of this study is the definition of the role of IL-10 gene polymorphism in relation to the quantitative level of this cytokine in the course of herpes zoster in adults (tendency to relapses, formation of a certain range of complications, etc.).

Conflicts of interest: authors have no conflict of interest to declare.
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