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ANALYSIS OF CLINICO-MORPHOLOGICAL AND MOLECULAR-GENETIC MARKERS IN PATIENTS WITH CHRONIC DERMATOSIS FOLLOWED BY FACE SKIN ATROPHY

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ABSTRACT

Objective: to identify associations between clinico-morphological and molecular-genetic markers in skin biopsy on the basis of a complex analysis.

Material and methods. Skin punch-biopsies with a diameter from 1 till 4 mm were used as a material for research. To assess the morphological charcateristis of the skin, the histological analysis was carried out; to assess the level of gene expression, real-time PCR with reverse transcription was performed.

Results. It has been found that the presence of morphological alterations in the skin of patients with chronic dermatosis is associated with the levels of normalized expression of COL1A1 gene less than 100 % and/or gene COL1A2 gene less than 200 % and/or gene LOX less than 50 %.

Conclusion. Real-time PCR with reverse transcription can be used for objective assessment of the degree of skin alteration in patients with chronic dermatosis.

Key words: chronic dermatosis, skin morphotype, morphological feature, genes.

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АНАЛИЗ КЛИНИКО-МОРФОЛОГИЧЕСКИХ И МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИХ МАРКЕРОВ У ПАЦИЕНТОВ С ХРОНИЧЕСКИМИ ДЕРМАТОЗАМИ, СОПРОВОЖДАЮЩИМИСЯ АТРОФИЕЙ КОЖИ ЛИЦА

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РЕЗЮМЕ

Цель исследования: на основании проведения комплексного анализа установить ассоциации между клинико-морфологическими и молекулярно-генетическими маркерами в биоптатах кожи.

Материал и методы. В качестве материала для исследования использовали панч-биопсий кожи диаметром от 1 до 4 мм. Для оценки морфологических характеристик кожи проводили гистологическое исследование; для оценки уровня экспрессии генов проводили ПЦР в режиме реального времени с обратной транскрипцией.

Результаты. Установлено, что наличие морфологических изменений в коже пациентов с хроническими дерматозами ассоциировано с уровнями нормализованной экспрессии гена COL1A1 менее 100 %, и/или гена COL1A2 – менее 200 %, и/или гена LOX – менее 50 %.

Заключение. Метод ПЦР в режиме реального времени с обратной транскрипцией можно использовать для объективной оценки степени изменений в коже у пациентов с хроническими дерматозами.

Ключевые слова: *хронический дерматоз, морфотип кожи, морфологическая характеристика, гены.*

ДЛЯ ЦИТИРОВАНИЯ:
Костюк СА, Шиманская ИГ, Руденкова ТВ, Полуян ОС, Глинкина ТВ. Анализ клинико-морфологических и молекулярно-генетических маркеров у пациентов с хроническими дерматозами, сопровождающимися атрофией кожи лица. *Проблемы Здоровья и Экологии.* 2020;64(2):136-142.

Introduction

In recent years, the increase in the number of patients with chronic dermatoses occurred with skin atrophy, as well as the existence of a set of unresolved issues related to etiology, pathogenesis and treatment methods, makes this pathology an important issue of modern healthcare [1].

Collagens are proteins deposited in the extracellular matrix where the most of them form supramolecular assemblies. Collagens

implement structural roles and promote to organization, mechanical properties and shape of tissues. Collagen accumulation is a characteristic of most fibrotic processes including the skin. During skin deseases the dermis, which comprised of extracellular matrix with scattered fibroblasts and bolstered by an interwoven network of collagen and elastin fibers, alter volume and mechanical properties [1-2].

There are a lot of signalling pathways leading to augmented collagen production by fibroblasts. The ability to obtain gene expression profiles from damaged tissue provides an opportunity to identify relevant gene pathways. In 2015 Inkeles MS an collegs show integration of IFN-regulated gene with skin deseases. Variable points in the inflammatory and cytokine networks known to drive chronic skin deseases, it may shape clinical course and treatment responses [1].

One of the relevant objectives is to determine the list of molecular genetic markers for a standardized and objective assessment of changes in the deep layers of the skin of patients with chronic dermatoses occurred with atrophy. Study and complex analysis of clinical data, morphological characteristics and normalized gene expression levels controlling the synthesis and maturation of collagen and elastin in the skin of patients with chronic dermatoses occurred with atrophy will allow establishing the presence of a possible association between these markers and defining molecular genetic criteria for assessment patient's skin.

Objective

To establish associations between clinical, morphological and molecular genetic markers in skin biopsies on the ground of a complex analysis.

Material and methods

The study group included patients (n = 224) with the following nosological forms of the disease: L90 (atrophic skin lesions), L93 (lupus erythematosus), L94 (other localized connective tissue changes), L43 (lichen ruber planus), L57.4 (age adermotrophia).

During the study, the patients were divided into groups according to the nosological forms of the disease as follows: group 1 – patients with limited forms of scleroderma (n = 101), group 2 – patients with discoid lupus erythematosus (n = 32), group 3 – patients with age adermotrophia (n = 91).

During clinical and morphological studies, an assessment of the nature of atrophic skin changes, as well as the study of morphological markers of pathological processes occurred with skin atrophy was performed.

During the study, a previously developed assessment scale [3] was used to visually assess the degree of skin atrophy, in which the following indicators were considered: skin morphotype, thickness of subcutaneous fat, the degree of ptosis.

In order to assess the morphological characteristics of atrophic skin changes histologic study was performed. The object of the study was a skin biopsy material obtained when performing punch biopsies with a diameter of 1 to 4 mm. The assessment of morphological parameters was performed using an optical light microscope Leica DC 200, at magnifications of 50x, 100x, 200x, 400x.

The obtained biopsy material was fixed and embedded in paraffin. Step histologic sections 4 microns thick obtained from paraffin blocks were dewaxed in xylene, dehydrated in alcohols of increasing concentration and stained with hematoxylin and eosin according to the standard technique.

In addition to routine hematoxylin and eosin staining, additional histochemical staining methods according to Hart-Weigert (to evaluate changes in elastic fibers), according to Masson (to detect changes in collagen fibers) [4] were used. Microscopy of sections stained with hematoxylin and eosin and additional techniques evaluated the nature of the identified changes in the epidermis, as well as in the dermis (the state of collagen and elastic fibers, the presence of elastosis).

When conducting molecular genetic studies, punch biopsies of the skin were used as biological material, which were stored using RNA reagent later (Sigma). RNA isolation was performed using the PureLink RNA MicroKit (Invitrogen). Then RNA was subjected to reverse transcription using the SuperScript III kit Reverse Transcriptase (Invitrogen), dNTP (Invitrogen) and Ribonucleaseinhibitor (Invitrogen). The obtained DNA was used for setting TaqMan real time PCR. Real-time PCR was performed using Quick-LoadTaq 2X MasterMix (Praymteh, the Republic of Belarus) selected pairs of primers and probes for each gene, including house-keeping gene (HGUS), on a thermal cycler «Rotor-Gene-6000» («Corbettresearch», Australia). In each tube, amplification of one of the studied genes controlling the synthesis and maturation of collagen and elastin (COL1A1, COL1A2, LOX, P3H1,

ELN) and house-keeping of the HGUS gene, relatively to which the normalization was performed, according to the threshold cycles (Ct) of the studied genes, to compare expression levels was performed [5].

Statistical analysisof obtained results using the computer program «Statistica» 10.0 was carried out. During the analysis, nonparametric methods of statistical analysis, univariate and multivariate analyses were used.

Results and discussion

Available literature sources do not mention any research of collagen and elastin gene expression in patients with skin deseases. So we try to analyse and describe our results of associations between clinical, morphological and molecular genetic markers in skin biopsies on the ground of a complex analysis.

In the examined groups of patients, mixed, fine-wrinkled, and gravitational skin morphotypes were identified (Table 1). In patients of all groups, a mixed skin morphotype prevailed (from 69.23% in patients of group 3 to 86.14% in patients of group 1).

During further analysis the degree of changes of the skin morphotype, the change of the thickness of subcutaneous tissue, the degree of manifestation of ptosis were evaluated. All indicators were evaluated according to the scale from 0 to 3 score.

In all patients of group 1 (n = 101), the degree of skin morphotype changes was estimated at 2 scores. The degree of changes of subcutaneous fat in patients of this group was estimated at 2 scores in 4.95 % of patients (n = 5); in other 95.05 % of patients (n = 96), the degree of subcutaneous fat ranged from 0.5 to 1.5 cm and was estimated at an average of 1 score. The degree of ptosis in 4.95 % of patients (n = 5) was estimated at 0 scores; in 95.05 % of patients (n = 96) – 1 score.

In group 2 (n = 32) the degree of skin morphotype was estimated at 2 scores in 90.63 % of patients (n = 29); in 9.38 % of patients (n = 3) – at 3 scores. The degree of changes in subcutaneous fat in all patients (n = 32) was estimated at 1 score. The degree of ptosis in 18.75 % of patients (n = 6) was estimated at 1 score; in 81.25 % of patients (n = 26) – 2 scores.

Table 1 – The frequency of detection of various skin morphotypes in the examined groups of patients

Skin morphotype	The frequency of detection of sign (% (n))		
	Group 1 (n = 101)	Group 2 (n = 32)	Group 3 (n = 91)
Mixed	86.14 (87)	81.25 (26)	69.23 (63)
Fine-wrinkled	10.89 (11)	12.5 (4)	20.88 (19)
Gravitational	2.97 (3)	6.25 (2)	9.89 (99)

The degree of skin morphological changes in patients of group 3 (n = 91) was estimated at 2 scores in 89.01 % of patients (n = 81); 3 scores – in 10.99 % of patients (n = 10). The degree of changes in subcutaneous fat in 14.29 % of patients in this group (n = 13) was estimated at 1 score; in 82.42 % of patients (n = 75) – at 2 scores and in 3.29 % of patients (n = 3) – at 3 scores. The degree of ptosis in 95.61 % of patients (n = 87) was estimated at 2 scores; in 4.39 % of patients (n = 4) – at 3 scores.

During the evaluation of the morphological characteristics of the skin, a study of skin atrophy in the form of epidermis thinning and the smoothness of the dermal papillae was made. Results obtained during this stage are presented in Table 2.

Table 2 – The presence of signs of atrophy of the epidermis in the examined patients (n = 224)

Morphological characteristic	Detection rate	
	n	%
The presence of signs of epidermis atrophy	27	12.05
The absence of signs of epidermis atrophy	197	87.95

Symptoms of epidermis atrophy were detected in 12.05 % (n = 27) among all examined patients, of which 9 patients were in group 1; 4 patients – in group 2; 14 patients – in group 3.

To characterize the state of collagen fibers, its thickening and homogenization were evaluated taking into account localization in certain components of the dermis (along its entire length, foci) when stained with hema-

toxylin and eosin, as well as with additional Massonstaining.

Changes in the state of collagen fibers were revealed in all examined patients. During the study mainly focal thickening of collagen fibers in the dermis was established in patients of all groups (from 61.54 % to 84.38 %) (Table 3). The thickening of the collagen fibers along its entire length was typical for patients in the group of 3-38.46% of cases (n = 35).

Table 3 – The frequency of detection of changes in collagen fibers in the dermis in the examined groups of patients

Type of lesion	Group 1 (n = 101)		Group 2 (n = 32)		Group 3 (n = 91)	
	n	%	n	%	n	%
Focal thickening	81	80.19	27	84.38	56	61.54
Along its entire length	10	9.91	5	15.62	35	38.46

During the assessment of solar elastosis in the dermis in patients of group 1, the absence of solar elastosis was observed in 21.78 % of cases (n = 22); minimal solar elastosis were observed in 67.39 % of cases (n = 61); phenomena of solar elastosis of moderate degree – in 17.82 % of cases (n = 18). In patients of group 2, solar elastosis were observed more o less in all cases: the minimal solar elastosis were noted in 25.0 % of cases (n = 8); solar elastosis of moderate degree – in 46.88 % of cases (n = 15); marked solar elastosis – in 28.13 % of cases (n = 9). Among the patients of the group 3, solar elastosis was also noted in 100 % of cases: in 7.69 % of cases (n = 7) – the minimum effects of solar elastosis; in 92.31 % of cases (n = 84) – moderately solar elastosis.When using additional Hart-Weigerthistochemical staining for an objective assessment of the state of elastic fibers, it was found that patients had: fragmentation and reduction of elastic fibers, reduction in the number of elastic fibers until disappearing, compaction of elastic fibers in the upper third of the dermis (Table 4).

Table 4 – The frequency of detection of changes in the elastic fibers of the dermis in the examined groups of patients

Nature of change	The frequency of detection of changes (n (%))		
	Group 1 n = 101)	Group 2 (n = 32)	Group 3 (n = 91)
Elastic fiber fragmentation	–	50.0 (16)	86.81 (79)
Fragmentation and reduction of elastic fibers	76.24 (77)	28.13 (9)	5.49 (5)
Lowering in elastic fibers up to disappearance	10.89 (11)	21.88 (7)	–
Compaction of elastic fibers in the upper third of the dermis	12.87 (13)	–	7.69 (7)

In group 1, fragmentation and reduction of elastic fibers were predominantly detected, however, cases of disappearance or compaction of elastic fibers were also detected.In patients of groups 2 and 3, fragmentation of elastic fibers was predominantly noted, the frequency of other changes was significantly lower. All this allows us to conclude that significant violations of the processes of synthesis and maturation of elastin in patients of group 1 were observed.

When assessing genes normalized expressionlevel controlling the synthesis and maturation of collagen and elastin using developed multiplex real-time PCR method, the values for genes COL1A1, COL1A2, LOX, P3H1, ELN were determined (Table 5). The calculated normalized expression levels ranged from 0 for gene ELN to 1422.6 for gene COL1A2.

Based on the values of normalized expression levels, we can conclud that the ELN gene is reduced in all the examined patients, since All calculated values of normalized expression levels were less than 100 % and ranged from 0 to 84.1 %.There were no significant differences in the values of normalized expression levels of all the studied genes between the groups of examined patients (Mann-Whitney test, $p > 0.05$).

Analysis of connection between the clinical signs of skin lesions (morphotype ≥ 2 scores, changes in subcutaneous fat ≥ 1 scores, ptosis ≥ 1 score) and morphological changes (atrophy of the epidermis, thickening and homogenization of collagen fibers, elastosis, change of elastic fibers) were performed using contingency tables and x2-Pearson criterion. As a result, a significant

association between clinical manifestations and morphological characteristics in patients with chronic dermatosesoccurred with skin atrophy ($p < 0.05$) was found.

Then, an analysis of the connection between the genes normalized expression level, controlling the synthesis of collagen and elastin (COL1A1, COL1A2, LOX, P3H1, ELN) and the morphological characteristics of the skin in the examined patients with chronic dermatoses was made. The morphological characteristics of the skin were divided into 2 groups: the presence of changes (atrophy of the epidermis; thickening or homogenization of collagen fibers; elastosis; condition of elastic fibers) of any degree against the absence of changes. For the ELN gene, the sign was considered as nominal, since its expression in 43.75% of cases was equal to 0.

According to the results of a single-factor analysis, we can conclude that the possibility of epidermis atrophy in patients with chronic dermatoses is significantly higher with a decrease in the expression of genes COL1A1, COL1A2, LOX (Table 6). For other genes, no effect of normalized expression level on the presence of epidermis atrophy was revealed ($p > 0.05$).

Then, as a ranking factor, the criterion of the presence or absence of thickening or homogenization of collagen fibers was used.According to the results of statistical analysis, we can conclud that the chance of changes in the structure of collagen fibers in patients with chronic dermatoses is significantly higher with a decrease in the expression of genes COL1A1, COL1A2, LOX.

For other genes, no effect of normalized expression level on the presence of thickening or homogenization of collagen fibers ($p>0.05$) was detected. At the next stage, the criteria for the presence or absence of elastosis in patients was used as a ranking factor.

According to the results of statistical analysis, we can conclude that the chance of elastosis in patients with chronic dermatoses is significantly higher with a decrease in the expression of genes COL1A1, COL1A2, LOX. For other genes, no effect of genes normalized expression level on the presence of thickening or homogenization of collagen fibers ($p > 0.05$) was detected.

Table 5 – Values of gene normalized expression level controlling the synthesis and maturation of collagen and elastin in the examined groups of patients

Gene	% gene normalized expression level (Me (Q_{25}/ Q_{75}))		
	Group 1 (n = 101)	Group 2 (n = 32)	Group 3 (n = 91)
COL1A1	124.5 (17.9/576.2)	137.2 (22.6/614.2)	95.7 (12.4/427.6)
COL1A2	451.7 (92.1/1283.2)	463.1 (103.7/1422.6)	254.3(71.4/862.7)
LOX	78.6 (8.7/267.4)	84.1 (22.6/308.7)	73.1 (7.2/221.5)
P3H1	15.3 (10.2/63.4)	16.1 (9.4/67.2)	14.8 (7.9/55.6)
ELN	34.3 (0.0/61.4)	42.1 (0.0/84.1)	26.1 (0.0/56.9)

Table 6 – Association of gene expression controlling the synthesis of collagen and elastin, with atrophy of the epidermis, with thickening or homogenization of collagen fibers and with elastosis

Epidermal atrophy			
Gene	Changes (n = 197)	No changes (n = 27)	p
COL1A1	87.1 (16.3/133.4)	286.2 (149.7/627.6)	0.047
COL1A2	145.6 (84.3/227.1)	621.6 (352.1/1520.8)	0.042
LOX	54.7 (3.4/67.9)	62.5 (49.7/311.4)	0.039
P3H1	15.4 (10.2/62.7)	16.3 (11.5/30.8)	0.243
ELN>0.n (%)	109 (55.33%)	17 (62.96 %)	0.511
Collagen Fiber Changes			
Gene	Changes (n = 214)	No changes (n = 10)	p
COL1A1	85.2 (13.3/137.2)	289.2 (151.7/626.6)	0.044
COL1A2	141.6 (82.3/215.3)	630.1 (349.1/1489.4)	0.047
LOX	52.9 (3.7/69.5)	63.5 (47.6/315.6)	0.032
P3H1	14.8 (10.1/64.3)	15.6 (12.5/32.5)	0.415
ELN>0.n (%)	124 (57.94 %)	6 (60.0 %)	0.324
Elastosis			
Gene	Changes (n = 202)	No changes (n = 22)	p
COL1A1	84.8 (14.1/134.6)	290.1 (153.4/627.1)	0.031
COL1A2	142.1 (83.3/217.1)	632.1 (347.1/1491.6)	0.027
LOX	54.7 (3.9/67.5)	65.2 (49.1/314.2)	0.044
P3H1	14.6 (10.4/64.8)	14.2 (13.7/35.2)	0.357
ELN>0.n (%)	109 (53.96%)	13 (59.09%)	0.241

When using the state of elastic fibers as a ranking factor, no effect of the genes normalized expression level of the genes COL1A1, COL1A2, LOX, P3H1, ELN on this morphological index was revealed ($p > 0.05$).

When conducting multivariate analysis, it was found that the chance of morphological changes (epidermis atrophy and/or collagen fibers changes and/or elastosis) in the skin of patients with chronic dermatoses increased with a decrease in COL1A1 gene expression less than 100% and/or COL1A2 gene less than 200% and/or the LOX gene less than 50 % (Table 7).

Table 7 – Results of a multivariate analysis of the effect of gene expression COL1A1, COL1A2, LOX on morphological changes in skin of patients with chronic dermatoses

Variable	b	OR (95% CI OR)	p
COL1A1	0.11	1.20 (1.03-1.34)	0.026
COL1A2	1.12	6.13 (1.07-9.04)	0.034
LOX	2.42	6.31 (2.57-9.55)	0.027

Conclusion

During the study a reliable association of clinical manifestations and morphological characteristics of skin biopsy specimens in patients with chronic dermatoses accompanied by facial skin atrophy was determined.

It has been established that the presence of morphological changes in the skin of patients with chronic dermatoses accompanied by facial skin atrophy is associated with COL1A1 gene normalized expression level less than 100 % ($p < 0.05$) and/or COL1A2 gene less than 200 % ($p < 0.05$) and/or the LOX gene less than 50 % ($p < 0.05$).This allows us to recommend the use of real-time PCR method for an objective assessment of changes in patients skin with chronic dermatoses without conducting time-consuming and subjective studies using the histological method.

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