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Plasma level of IL-8 in patients with psoriasis and its correlation with psoriasis area and severity index and the clinical type of the disease

Stężenie IL-8 w osoczu chorych na łuszczycę w zależności od PASI i typu klinicznego choroby

Clinical skin changes in psoriasis originate as a result of mild proliferation of epidermis, vascular disorders of surface system of skin vessels and infiltrations of the dermis (3). A special phenomenon occurring in psoriasis is migration of inflammatory cells via elongated papillae and formation of so-called Munro's microabscesses in the horny layer. It was reported that high amounts of arachidonic acid derivative present in the epidermis and the C3a and C5a components of complement as well as considerable amounts of IL-8 produced mainly by fibroblasts, have chemotactic influence on neutrophil granulocytes. A result of infiltration and neutrophil activation is the release of a considerable amount of proteases - lysosomal enzymes whose action sustains the disease (5). The infiltrating lymphocytes in the papillary layer of the dermis play a part in triggering various mechanisms of activation followed by down-regulation mechanisms (5, 8, 9).

IL-8 is produced by a variety of cell types, including monocytes, infiltrating mononuclear cells and keratinocytes after an inflammatory stimulus (3). Studies on the participation of IL-8 in the pathogenesis of psoriasis showed the increased level of IL-8 mRNA in lesional psoriatic epidermis (3, 6). Nickoloff et al. (6) found that in media conditioned by keratinocytes from psoriatic patients, both symptomless skin and psoriatic plagues, the amount of interleukin-8 was 10-20 times higher. Increased IL-8 R have also been detected in psoriatic epidermis (3,6). In psoriasis the increased number of IL-8 receptors was found, which may - besides elevated cutaneous IL-8 concentrations - contribute to the intraepidermal accumulation of PMNL in psoriasis (1). Highly elevated

amounts of IL-8 were found in psoriatic scales. Schröder et al. reported that the amounts of both NAP-1/IL-8 and gro-α MGSA in lesional psoriasis material were 150-times increased (3, 9).

There is a great deal of evidence to suggest IL-8 be an important factor influencing the topical development of psoriasis lesion. Most immunological topical activisations are reflected in the degree of concentration of proinflammatory factors in blood. So far the concentration of IL-8 in the plasma of psoriatic patients has been only briefly studied. IL-8 concentration can be regulated by the expression of specific IL-8 RA and IL-8RB receptors on neutrofils and neutrophil-like cells. In contrast to the IL-RA and IL-8RB receptors which have a narrow ligand specificity, the multispecific receptor (CK) expressed by human erythrocytes has been shown. The erythrocyte CK receptor was shown to be Duffy blood-group antigen. The receptor, thanks to its ability to bind IL-8 may at the same time regulate IL-8 concentration in blood (4).

Although aware of a number of factors involved in forming the actual level of IL-8 concentration in plasma, we took up the task of determining the level of IL-8 in the plasma of psoriatic patients in relation to the extent and intensity of the disease expressed by PASI index and the duration time of the relapse. Activation of the proinflammatory reactions characterizes the first acute period of relapse which gives way to chronic phase accompanied by the gradual recession of proinflammatory reaction.

The aim of the work is to answer the question if the IL-8 plasma concentration depends on the duration of the disease's relapse, extension and intensity of the disease process evaluated by the PASI score scale.

MATERIAL AND METHODS

We determined IL-8 plasma levels in 60 patients with psoriasis and in 10 control subjects. 10 people from the control group were of mean age 34.2±6.7 years. The patients were divided into two groups, with longer and shorter duration of the disease's relapse. The first group with acute psoriasis (relapse duration up to one month) consisted of 20 patients, mean age 34.9±10.6 years. The second group (with longer relapse duration - more than one month - has been determined as chronic psoriasis) consisted of 40 patients, mean age 37.4±11.1 years. The study was conducted with a consent of Local Ethical Committee.

The IL-8 plasma levels were determined with the use of EISA-kit (R&D Corporation). This method, like most immunoenzymatic methods, helps determine the concentration of molecules in the examined material, failing to evaluate their biological activity. We examined a correlation between IL-8 and the psoriasis area and severity index (PASI). PASI is a scale in which the following parameters are considered: erythema, infiltration, exfoliation, lesional areas separately for the head, trunk, upper and lower

limbs. Next, the total score is multiplied by appropriate mathematical indicators for each of 4 areas of the body, and summed up.

STATISTICAL METHODS

Cytokine values obtained in plasma were presented as arythmetic mean ±SD. Student's t-tests and Cochran's-Cox's tests were used to compare mean values. Correlation was detected by means of Pearson's coefficient.

RESULTS

The results of the study are presented in Tables 1-3. IL-8 concentration varied from 0 to 261 pg/ml, mean for all patients 36.3±48.6 pg/ml, and in the control group from 7 to 53.0 pg/ml, mean 23.9±17.6. PASI was from 16.2 to 70.2, mean 25.7±9.8 (values have not been shown).

Table 1. The mean IL-8 plasma concentration pg/ml and PASI score in psoriasis groups and controls

Groups	Duration of relapse intervals	n	IL-8 concentration mean± SD	Statistical significances of IL-8 concentration	PASI score	Statistical significance of PASI score results
Psoriasis	<1 month	20	72.1±67.8	p1=0.03 p2=0.00001	21.28± 3.8	NS
	>1 month	40	18.5±18.7	NS	24.2±4.4	
Controls	-	10	23.9±17.6	NS	0	-

p1- psoriasis vs controls, p2- psoriasis < 1 month vs psoriasis > 1 month

The results of statistical analysis concerning the comparison of IL-8 concentration in the control group, the group with acute psoriasis and chronic psoriasis, are presented in Table 1. IL-8 concentration in blood plasma in the acute psoriasis group is significantly higher than in the control group (p1=0.03), while in the group with chronic psoriasis the

mean IL-8 concentration does not differ from the mean concentration in the control group (18.5±18.7 vs 23.9±17.6 pg/ml).

The table presents the results of statistical analysis concerning IL-8 concentration in the patients' groups with the respect to the relapse duration. The group with "acute" psoriasis is characterized by significantly higher IL-8 concentration in blood plasma in comparison to the group of "chronic" psoriasis, p2=0.00001. However, no statistical difference was observed in relation to the analysis of PASI score with the respect to the relapse duration. (acute psoriasis 21.28±3.8 vs chronic psoriasis 24.2±4.4), p NS (Table 2).

Table 2. Correlation between PASI score and IL-8 plasma concentration in psoriatic patients

Correlation between PASI score and IL-8	Duration of relapse intervals	n	Pearson's - r coefficient	p
	< 1 month	20	(-) 0.050	>0.80
	> 1 month	40	(+) 0.065	>0.60

Table 3. The IL-8 means in dependence on groups of type disease: guttata, nummularis and/or placibus and erythrodermic type

Type of disease	n	IL-8 mean ±SD	Statistical significance
Guttata	28	46.4± 65.1	NS
Nummularis and/or placibus	27	29.6 ± 51.4	NS
Erythrodermic type	5	58.6 ± 40.6	P1<0.03
Controls	10	23.9 ±17.6	-

Table 2 shows the results of statistical analysis of the correlation between PASI score and IL-8 plasma concentration calculated with Pearson's coefficient. We have examined the correlation between IL-8 and the severity index of psoriasis and have not found any correlation.

The analysis of IL-8 concentrations conditioned by the type of disease: guttata, nummularis and/or plaque and erythrodermic type has been carried out. This is important since the guttata type is often precipitated by infections which may well raise IL-8 levels (10). The presented results (Table 3) show the maximum statistically significant IL-8 concentration in the group with erythroderma (58.6±40.6, P1<0.03).However, the raised concentrations in the patients with guttata type 46.4±65.1 pg/ml did not have statistically significant characteristics.

DISCUSSION

The role of locally produced IL-8 in psoriatic inflammation have been studied in several aspects. Nickoloff et al.(6) concluded that angiogenesis in psoriasis might be due to an overproduction of IL-8 by keratinocytes and deficiency of thrombospondin-1 (a matrix glycoprotein is known to have an inhibitory action on angiogenesis). Its chemotactic activity on human neutrophils is mediated via specific receptors for IL-8 on PMNL (1). Activation of PMNL enzymes may cause an increased expression of the surface chemotactic receptors or accelerate transmission of intercellular stimuli. The elevated surface density of IL-8 receptors was found in psoriatic patients (1). The increased release of cytokines may be selectively responsible for starting oxidation processes in polynuclear cells. In addition, IL-8 has been reported to stimulate the proliferation of keratinocytes (1, 3). After the treatment with neutralizing antibodies to IL-8, the suppression of the chemotactic activity of neutrophils was observed (2). Teranishi et al. studied the spontaneous production of IL-8 in monocytes of peripheral blood in patients comparing to the control, as well as the elevated IL-8 serum concentration in psoriatic patients (10). Sticherling et al. (9), using either the assay from their laboratory or three commercial ELISAs, found no correlation between serum IL-8 levels and disease severity at any stage of the disease.

In our work the highest IL-8 plasma concentration was found in the group with acute form of psoriasis (relapse duration up to one month), versus the concentration in the control and chronic psoriasis group (7). However, the experiments done so far do not let us exclude the assumption that increased IL-8 levels affect the reccurrence of the disease. We have not found any correlation between IL-8 and the severity (PASI score) of psoriasis. These data suggest that the different mechanisms existing during acute and chronic psoriasis relapse may influence IL-8 plasma levels. Comparative analysis on IL- and Gro-α -expression may very well explain neutrophil trafficking from the vessel compartment to the upper epidermis and may be valid for other inflammatory procesess (3).

In the synthesis of IL-8, the way in which the immune system activates and stops it is important. There may be several immunomodulating mechanisms, such as: exfoliation of IL-8 receptors, existing soluble receptors for inflammatory cytokines, high-affinity autoantibodies (aAb) to inflammatory cytokines, autoinflammatory cytokines (like TGF-ß,

IL-10), inhibition by PGE2 (2). The presence of specific, high-affinity antibodies (aAb) to different inflammatory cytokines in human immunoglobulin and in sera of normal individuals and patients with immunoinflammatory disorders, suggests that these antibodies may be involved in physiological and pathological process (2).

Because of the existence of down-regulation mechanisms, it can be presumed that if the disease's relapse is longer, the dependences between clinical parameters and IL-8 concentration in blood plasma may not be stated. The duration of absence of further correlations with IL-8 is consistent with the time of production of the respective immunoregulatory mechanism. In some patients natural regulation may occur, with a slightly weaker inflammatory reaction.

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STRESZCZENIE

Interleukina-8 jest jedną z cytokin chemotaktycznych o właściwościach prozapalnych i prowzrostowych produkowanych w łuszczycy przez naciekające komórki jednojądrzaste. Podjęliśmy próbę określenia stężenia IL-8 w surowicy krwi chorych na łuszczycę z uwzględnieniem czasu trwania nawrotu i ciężkości schorzenia wyrażonej w skali PASI (Psoriasis Area and Severity Index). Badaliśmy stężenie IL-8 w surowicy krwi 60 pacjentów z łuszczycą i 10 zdrowych ochotników z grupy kontrolnej. Chorych na łuszczycę podzielono na dwie podgrupy w zależności od czasu trwania nawrotu. Podgrupę pierwszą stanowili pacjenci z ostrą łuszczycą (AC - acute psoriasis), u których czas trwania nawrotu wynosił mniej niż miesiąc. W podgrupie łuszczycy przewlekłej (CP - chronic psoriasis) znaleźli się pacjenci, u których choroba trwała dłużej niż miesiąc. Stężenie IL-8 w surowicy oznaczano metodą ELISA przy pomocy gotowych zestawów firmy R&D. Pacjenci w grupie „ostrej łuszczycy" (AC) mieli znacznie wyższe stężenia IL-8 (72,1±67,8 pg/ml) niż w grupie łuszczycy przewlekłej (CP) (18,5±18,7pg/ml) i w grupie kontrolnej (C) (23,9±17,6 pg/ml). Nie stwierdziliśmy istnienia jakiejkolwiek korelacji pomiędzy nasileniem schorzenia określanym w skali PASI i stężeniem IL-8 w surowicy. Nasze wyniki sugerują, że „ostremu" okresowi łuszczycy mogą towarzyszyć wysokie stężenia IL-8.