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PREDICTIVE VALUE OF INFLAMMATORY CYTOKINES IN PREDICTING THE RISK OF PROLIFERATIVE DIABETIC RETINOPATHY

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A retrospective clinical and immunological study determined the diagnostic value of inflammatory cytokines in predicting the development of proliferative diabetic retinopathy. 82 patients with diabetes mellitus were divided into two groups: group 1 – 40 patients without developing proliferative complications of diabetic retinopathy and group 2 – 42 patients with the transition of non-proliferative diabetic retinopathy to proliferative one. In the blood of patients of the second group, there was a significantly higher level of concentration of the cytokines TNF-α (Pu=0.001), IL-1β (Pu<0.001), IL-8 (Pu<0.001) in the absence of significant changes in the cytokine IL-4 (Pu=0.094; Pu=0.073). The distribution of the balance of cytokines towards pro-inflammatory ones indicates the critical role of systemic inflammation along the type 1 T-helper pathway in the pathogenesis of proliferative diabetic retinopathy. The values of TNF-α cytokines above the level of 6.3 pg/ml (test sensitivity 71.4 %, specificity 65.0 %), IL-1β above 11 pg/ml (test sensitivity 69.0 %, specificity 87.5 %), IL-8 above 28 pg/ml (test sensitivity 81.0 %, specificity 65.0 %) can be used as criteria for predicting a high risk of developing proliferative diabetic retinopathy.

Key words: diabetic retinopathy, tumor necrosis factor-α, interleukin-1ß, interleukin-8, interleukin-4, prognosis criteria, inflammation.

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ПРЕДИКТОРНА ДІАГНОСТИЧНА ЦІННІСТЬ ЦИТОКІНІВ ЗАПАЛЕННЯ У ПРОГНОЗУВАННІ РИЗИКУ РОЗВИТКУ ПРОЛІФЕРАТИВНОЇ ДІАБЕТИЧНОЇ РЕТИНОПАТІЇ

У результаті ретроспективного клініко-імунологічного дослідження визначено діагностичну інформативність цитокінів запалення у прогнозі розвитку проліферативної діабетичної ретинопатії. 82 пацієнти з цукровим діабетом було поділено на дві групи: перша група – 40 пацієнтів без розвитку проліферативних ускладнень діабетичної ретинопатії; друга група – 42 пацієнти з переходом непроліферативної діабетичної ретинопатії до проліферативної. У крові пацієнтів другої групи достовірно відзначався вищий рівень концентрації цитокінів TNF-α (Pu=0,001), IL-1β (Pu<0,001), IL-8 (Pu<0,001) за відсутності значних змін цитокіну IL-4 (Pu=0,094) ; Pu = 0,073). Розподіл балансу цитокінів у бік прозапальних свідчить про важливу роль системного запалення по Т-хелперному шляху типу 1 в патогенезі проліферативної діабетичної ретинопатії. Значення цитокінів TNF-α вище за рівень 6,3 пг/мл (чутливість тесту 71,4 %, специфічність 65,0 %), IL-1β вище 11 пг/мл (чутливість тесту 69,0 %, специфічність 87,5 %) IL-8 вище 28 пг/мл (чутливість тесту 81,0 %, специфічність 65,0 %) можуть бути використані в якості критеріїв прогнозу високого ризику розвитку проліферативної діабетичної ретинопатії.

Ключові слова: діабетична ретинопатія, фактор некрозу пухлини-α, інтерлейкін-1ß, інтерлейкін-8, інтерлейкін-4, критерії прогнозу, запалення

Diabetic retinopathy (DR) is one of the common causes of irreversible blindness and visual impairment [13]. The mechanism of DR's development and transition from nonproliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR) has been studied in detail and is presented in numerous literature data [8, 9, 12]. The progression of DR and its transition to the proliferative stage in patients with diabetes mellitus (DM) is an ominous signal of deterioration in both ophthalmological status and general glycemic control. Chronic hyperglycemia, hypoxia, and inflammation are interrelated to trigger a cascade of pathological biochemical and immunological disorders, leading to damage to the microcirculatory bed of the retina [1] and the development of DR-specific clinical manifestations [15].

Despite the vast number of publications on the mechanism of development of DR and its treatment methods, the pathogenesis of DR is very complex and, in many specific aspects, requires the development of fundamentally new treatment measures and therapeutic targets. A milestone in treating PDR has begun from the end of the 20th century to the present day. It continues with the intravitreal administration of various drugs capable of binding the vascular endothelial growth factor (VEGF) molecule [14]. However, in addition to the proven activation of VEGF synthesis during DR development, publications in recent years have considered issues of detailed study of the role of other factors in the chain of links in DR pathogenesis [11]. In the triggering of pathological reactions that can lead to DR, one of the leading roles is played by inflammation and its active mediators – cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-17, IL-4, MCR-1, etc.) [3, 7]. Our previous study reported the development of diabetic maculopathy and PDR against increasing concentrations of the angiogenesis factor VEGF and inflammatory cytokines in the blood and tear fluid (TNF-α, IL-1β, IL-8) [10]. At the same time, a positive correlation was revealed between the

local and systemic levels of VEGF (r=0.333; p=0.031), between the central thickness of the macula and HbA1c, VEGF, TNF-α, IL-1β, IL-8 of a high degree of significance (p<0.001). Continuing study in this direction, it was of practical interest to calculate specific values of inflammatory cytokines to predict the possible risk of progression of NPDR to the proliferative stage.

The purpose of the study was to evaluate at the systemic level the informativeness and diagnostic significance of inflammatory cytokines (TNF-α, IL-1β, IL-8, IL-4) in predicting the risk of developing proliferative diabetic retinopathy.

Materials and methods. A retrospective longitudinal study based on clinical material from the National Center of Ophthalmology named after Academician Zarifa Aliyeva included 82 patients with diabetes. At the initial visit, all patients had a moderate stage of NPDR. The study did not include patients with severe NPDR at the initial visit. The study was conducted over a year in two groups of patients. The first group (I) included 40 patients without the transition of NPDR to PDR; in the second (II) – 42 patients with progression of NPDR to the initial stage of PDR within a year. It was of practical interest to assess the prognostic significance of inflammatory cytokines in the progression of NPDR to the initial stages of PDR.

After six months in group II, 64 % (27/42) progressed from NPDR to PDR, while in 36 % of 42 patients, DR persisted at the nonproliferative stage (15/42). After one year in group II, NPDR in 100 % of patients (42/42) developed into PDR. Exclusion criteria were any other pathology of the retina (except for NPDR), active inflammation of the eye and its adnexa, clouding of the eye's optical media, intraocular surgery or laser intervention within the last three months, autoimmune systemic diseases, and oncological diseases. There were no statistical differences between the groups regarding age, gender, or average duration of diabetes. The average age of patients in the first and second groups was 57.5±8.8 and 56.0±10.5 years (p=0.581). The relative and absolute number of men was 45 % (18/40) and 52 % (22/42) (p=0.507). The average duration of diabetes was 12.0±5.8 and 13.5±4.2 years (p=0.098). There was also no significant difference between the groups based on the type of diabetes (p=0.264): in group II, 52 % (22/42) of patients suffered from type I diabetes, and in group I – 40 % (16/40). In group II, the relative number of patients suffering from concomitant hypertension (71 % – 30/42), coronary artery disease (31 % – 13/42), nephropathy (41 % – 17/42) and neuropathy (57 % – 24/42) was slightly higher than in group I (60 % – 24/40, 23 % – 9/40, 25 % – 10/40, 55 % – 22/40) without statistical significance of this difference (p=0.278, p=0.391, p=0.138, p=0.846).

The study was conducted by the requirements of the Declaration of Helsinki after written informed consent of all patients who took part in it (approval of the Ethics Committee of the Azerbaijan Medical University, protocol No. 25).

To achieve this purpose, ophthalmological and immunological research methods were used. Ophthalmological research methods: determination of the best corrected visual acuity (BCVA) (Huvitz Chart Projector CCP-3100 (HUVITZ Co, LTD, South Korea), biomicroscopy of the anterior segment of the eye (TOMEY TSL-5000 slit lamp, TOMEY, Japan), tonometry (non-contact tonometer FT-1000, TOMEY, Japan), funduscopy (slit lamp TOMEY TSL-5000, TOMEY, Japan with Ocular High Mag 78D lens, Ocular Instruments Inc., USA), optical coherence tomography (OCT) (Cirrus optical coherence tomography HD-OCT 5000, Carl Zeiss Meditec AG, Germany), fluorescein angiography (FA) (Carl Zeiss FF450, Germany). Objective confirmation of the progression of NPDR in these patients was the presence of local ischemic zones on FA with increased microaneurysms, retinal hemorrhages, and newly formed vessels.

The immunological study included determining the level of pro-inflammatory cytokines TNF-α, IL-1β, IL-8, and anti-inflammatory cytokine IL-4 in blood serum (BS) using enzyme-linked immunosorbent assay kits (ELISA).

The results were statistically processed using the methods of variation, dispersion, and ROC analysis using MS Excel and IBM Statistics SPSS-26 software. The statistical significance of the differences was assessed at p<0.05.

Results of the study and their discussion. Table 1 presents comparative results of a study of the cytokine content in the BS in both groups of patients at their initial treatment and after a year.

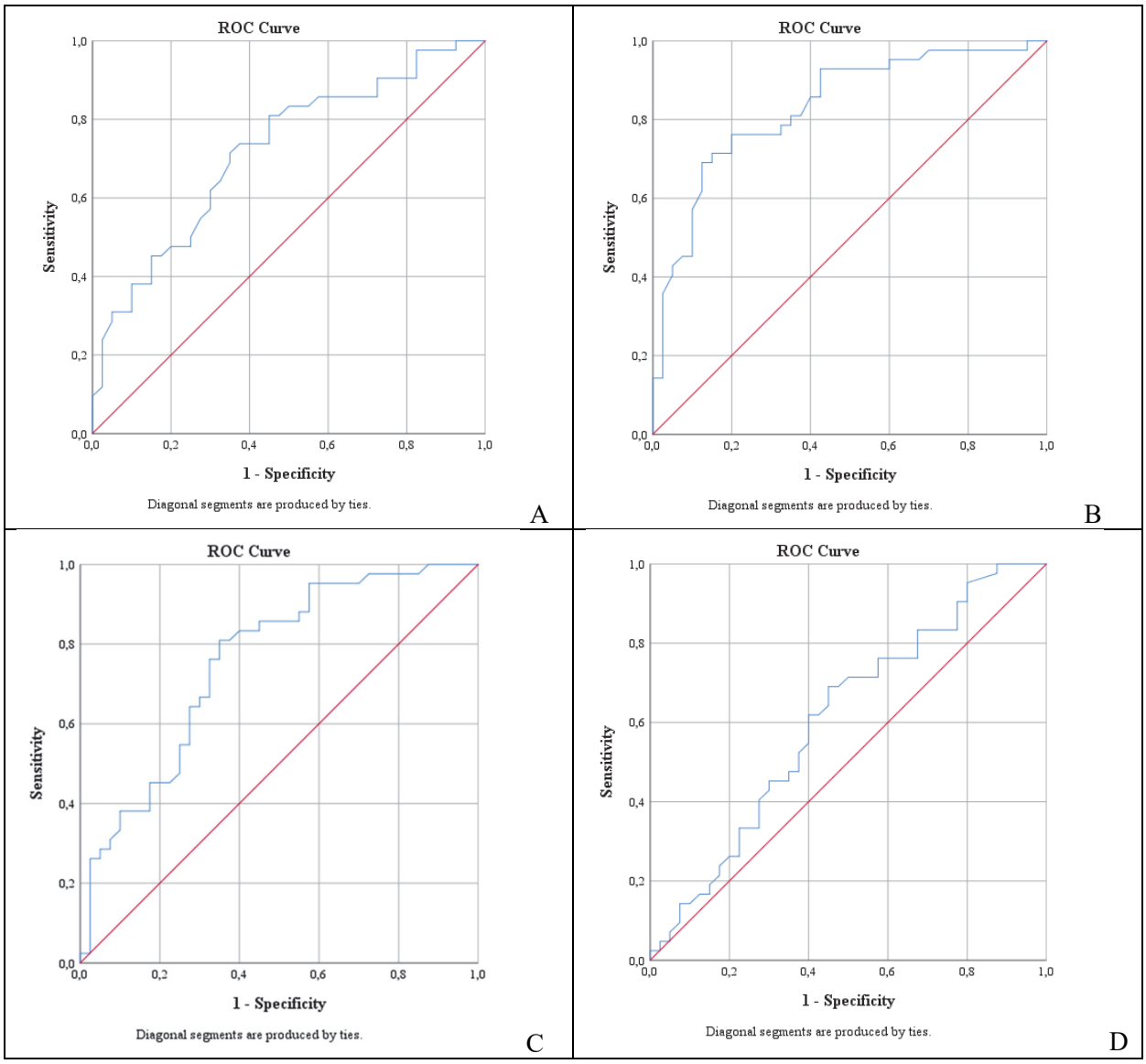
The results of a comparative assessment of pro-inflammatory cytokines indicate a significant increase in the average level of TNF-α (p<0.001; Pu=0.001), IL-1β (p<0.001; Pu<0.001), IL-8 (p<0.001; Pu<0.001) in BS at the initial visit of patients in group II. After a year, all patients showed progression of NPDR to the initial stages of PDR. However, when comparing the content of the average level of anti-inflammatory cytokine IL-4 in both groups of patients at the stage of NPDR at the initial treatment, no significant difference was found (p=0.180; Pu=0.094).

Table 1

Results of a comparative analysis of the cytokines' content in BS at initial treatment and after a year (pg/ml)

Cytokine	Group	Mean	Std. Dev.	Std. Er.	95 % Confidence Interval for Mean		F	p	Pu
					LB	UB			
At the initial visit									
TNF-α	I	5.3	2.9	0.5	4.3	6.2	13.275	<0.001	0.001
	II	7.7	3.2	0.5	6.7	8.7			
IL-1β	I	7.1	3.3	0.5	6.1	8.2	40.203	<0.001	<0.001
	II	12.1	3.7	0.6	11.0	13.3			
IL-8	I	22.6	15.6	2.5	17.6	27.6	20.580	<0.001	<0.001
	II	38.0	15.0	2.3	33.3	42.7			
IL-4	I	6.5	5.3	0.8	4.8	8.2	1.831	0.180	0.094
	II	8.1	5.1	0.8	6.5	9.7			
After one year									
TNF-α	I	5.3	2.6	0.4	4.4	6.1	28.581	<0.001	<0.001
	II	8.4	2.7	0.4	7.6	9.2			
IL-1β	I	7.3	3.2	0.5	6.3	8.3	64.196	<0.001	<0.001
	II	12.9	3.1	0.5	11.9	13.8			
IL-8	I	23.0	14.1	2.2	18.5	27.5	31.865	<0.001	<0.001
	II	40.5	13.9	2.1	36.1	44.8			
IL-4	I	6.7	5.0	0.8	5.1	8.3	4.066	0.047	0.073
	II	4.8	3.6	0.6	3.6	5.9			

Note: p – value of statistical difference according to Fisher; Pu – Mann-Whitney statistical difference value.



Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95 % Confidence Interval	
				Lower Bound	Upper Bound
TNF-α	0.719	0.056	0.001	0.609	0.829
IL-1β	0.833	0.045	0.000	0.744	0.921
IL-8	0.756	0.053	0.000	0.651	0.860
IL-4	0.607	0.063	0.094	0.484	0.730

Fig. 1. ROC curves of cytokines in BS during the progression of NPDR to the early stages of PDR: a) TNF-α; b) IL-1β; c) IL-8 d) IL-4. The table below the graphs presents the parameters of the areas under the ROC curves, indicating the reliability values of the sensitivity and specificity of the tests with 95 % CI.

A year later, in patients in group II, with the development of proliferative changes in DR, the trend with a significantly higher average level of proinflammatory cytokines TNF-α, IL-1β, IL-8 in the BS persists according to both Fisher and Mann-Whitney ($p<0.001$; $Pu<0.001$). While the average level of IL-4 in group II (4.8 pg/ml), being lower than in group I (6.7 pg/ml), was not statistically significant according to Mann-Whitney (Fisher $p=0.047$, Mann-Whitney $Pu=0.073$).

To assess the quality of cytokines' predictive significance and determine their sensitivity and specificity in predicting the development of proliferative changes in DR, a ROC analysis was carried out. The results are sequentially presented below in the form of four ROC curves of the studied cytokines in Fig. 1.

The results of the ROC analysis allow us to conclude the statistical significance of the sensitivity and specificity of the tests TNF-α ($p=0.001$), IL-1β ($p<0.001$), and IL-8 ($p<0.001$) in predicting the progression of NPDR to PDR. This cannot be noted for the anti-inflammatory cytokine IL-4; the sensitivity and specificity of the test were insignificant ($p=0.092$).

The next step was to determine the cut-off points in the coordinates of the ROC curves that were the most distant from the reference line with the highest total value of specificity and sensitivity. The results of calculating the specificity and sensitivity of each indicator for these points and the strength of its influence on the development of proliferative changes in diabetic retinopathy (dispersion test using Snedecor's F distribution) are presented in Table 2.

Table 2

Results of calculation of cut-off cytokines' points and ANOVA analysis of variance

Stat.	TNF-α	IL-1β	IL-8	IL-4
Limit value (cut-off)	> 6.3	>11	>28	>5.5
II (n)	42	42	42	42
++	30	29	34	29
Sn	71.4	69.0	81.0	69.0
±mp	7.0	7.1	6.1	7.1
I (n)	40	40	40	40
--	26	35	26	22
Sp	65.0	87.5	65.0	55.0
±mp	7.5	5.2	7.5	7.9
DV	56	64	60	51
%	68.3	78.0	73.2	62.2
±mp	5.1	4.6	4.9	5.4
pPV	68.2	85.3	70.8	61.7
±mp	7.0	6.1	6.6	7.1
nPV	68.4	72.9	76.5	62.9
±mp	7.5	6.4	7.3	8.2
LR+	2.04	5.52	2.31	1.53
	acceptable	good	acceptable	not applicable
LR-	0.44	0.35	0.29	0.56
	acceptable	acceptable	acceptable	not applicable
Odds ratio (95 % CI)	4.6 (1.8–11.8)	15.6 (5.0–49.0)	7.9 (2.9–21.6)	2.7 (1.1–6.7)
Fisher-Snedecor	12.308	39.255	22.220	5.021
p	0.001	<0.001	<0.001	0.028

Note: Sn – sensitivity; Sp – Specificity; DV – diagnostic value; ++ (--) – true-positive (negative) results; ±mp – 95 % confidence interval of the results obtained; pPV (nPV) – predictive utility of a positive (negative) result; LR+ (LR-) – likelihood-ratio test of a positive (negative) result; odds ratio (Odds ratio – OR) is a quantitative index of a relatively higher or less high risk of an event occurring in one group compared to the risk in another.

So, thanks to the analysis, it was found that with an increase in the content of inflammatory cytokines in the blood: TNF-α above the level of 6.3 pg/ml (test sensitivity 71.4 %, specificity 65.0 %, OR – 4.6 %; $p=0.001$), IL-1β above the level of 11 pg/ml (test sensitivity 69.0 %, specificity 87.5 %, OR – 15.6 %; $p<0.001$), IL-8 above the level of 28 pg/ml (test sensitivity 81.0 %, specificity 65.0 %, OR – 7.9 %;

p<0.001) a significantly high risk of progression of NPDR in the initial stages of PDR can be predicted. That is, these cytokine values can be used as biomarkers for predicting a high risk of developing PDR since the likelihood ratio (LR+) is assessed as "good" or "acceptable", and the ratio (LR–) is evaluated as "acceptable". For the cytokine IL-4, the 5.5 pg/ml cut-off point is not applicable for prognostic purposes.

In modern literature, the diagnostic value of increasing concentrations of inflammatory cytokines with worsening severity of DR is considered in various aspects [3, 5, 7]. Many publications are devoted to the comparative study of the content of cytokines TNF-α, IL-1β, and IL-8 in the blood and in various ocular substrates (tear fluid, chamber moisture, vitreous contents) at multiple stages of DR [2, 5].

Activation of macrophages, neutrophils, eosinophils, and endothelial cells stimulates the pro-inflammatory effect of TNF-a. This, in turn, enhances the proliferation of T and B cells, cytotoxic lymphocytes, and phagocytosis, induces the synthesis of IL-1, IL-6, IL-2, chemoattractants, adhesive molecules (ICAM-1, VCAM-1, etc.), and acute-phase proteins. TNF-a aggravates microcirculation disorders by promoting increased capillary permeability and disrupting the integrity of the vascular endothelium [6]. IL-1β is one of the main inflammatory cytokines, the increase of which is due to the activation of the immune response along the type 1 T-helper pathway and the development of inflammation and destruction processes. A proven fact is the weakening of retinal endothelial migration and capillary morphogenesis under the influence of TNF-α and IL-1β with increased expression of inducible NO-synthase. TNF-α and IL-1β are important in disrupting the blood-retinal barrier and stimulating apoptosis in PDR [5]. Hyperglycemia, a powerful trigger, stimulates the overexpression of IL-1β by the retinal endothelium in PDR. IL-1β, in turn, maintains its expression at a high level by autostimulating endothelial and macroglial cells. IL-8 is a potent chemoattractant, one of the active pro-inflammatory α-chemokines involved in regulating angiogenesis and the pathogenesis of various types of inflammation characteristic of metabolic syndrome. IL-8, an indicator of a violation of the integrity of the endothelium of diabetic vessels, is one factor in the formation of microvascular complications in PDR [2]. Our data are consistent with studies indicating a significant increase in these inflammatory cytokines at the systemic level during the development of PDR [2, 5, 6]. According to the results obtained, the progression of DR and the transition of NPDR to the proliferative stage occurs against the background of activation of systemic inflammation. This may be due to worsening hyperglycemic conditions and impaired diabetes compensation.

IL-4 is an inducer of antibody formation and one of the important links in the chain of autoimmune reactions. The authors of most studies, having not found significant changes in this cytokine during the development of PDR, conclude that the balance of cytokine production is shifted towards the immune response along the T-helper-1 mediated pathway in this microvascular complication of DM [4].

The novelty of the presented study is the calculation of specific values of TNF-α, IL-1β, and IL-8, which can be offered as systemic markers for predicting the risk of progression of NPDR to the initial stages of PDR. Detection of cytokine levels in the blood of a patient with NPDR that exceed critical values (TNF-α – 6.3 pg/ml, IL-1β – 11 pg/ml, IL-8 – 28 pg/ml) may indicate a high risk of developing PDR and the feasibility of preventive anti-inflammatory treatment. The results dictate the need for further extensive studies to study the effectiveness of specific therapy for DR aimed against increased expression of cytokines.

Conclusions

1. The development of PDR against the background of significant growth (p <0.001) and the distribution of the balance of cytokines towards pro-inflammatory ones (TNF-α, IL-1β, IL-8) indicates the critical role of systemic inflammation and the immune response along the type 1 T-helper pathway in the pathogenesis of proliferative complications of retinal damage in patients with diabetes.

2. The values of TNF-α cytokines above the level of 6.3 pg/ml (test sensitivity 71.4 %, specificity 65.0 %, OR – 4.6 %; p=0.001), IL-1β above the level of 11 pg/ml (test sensitivity 69.0 %, specificity 87.5 %, OR – 15.6 %; p<0.001), IL-8 above the level of 28 pg/ml (test sensitivity 81.0 %, specificity 65.0 %, OR – 7.9 %; p<0.001) can be used as criteria for predicting a high risk of PDR developing.

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BASEL-VANAGAITE-SMIRIN-YOSEF SYNDROME

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Basel-Vanagaite-Smirin-Yosef Syndrome is a rare syndrome of genetic mental retardation caused by an autosomal recessive mutation of the MED 25 gene. 112 case histories of patients aged 1 month-3 years old with seizures were analyzed. During observation symptoms, characteristic for Basel-Vanagaite-Smirin-Yosef syndrome were detected. By comparing the frequency of clinical symptoms in this patient with others, we found that this syndrome is more characterized by a combination of sparse eyebrows and hair, wide forehead, retrognathia, hypertelorism with malformations of the brain and heart, and for early diagnosis an approach based on deep research should be recommended. A multidisciplinary approach to symptom management and timely initiation of prophylaxis of complications can improve the quality of life of these patients.

Key words: Basel Vanagaite-Smirin-Yosef Syndrome (BVSYS), MED25 gene, autosomal recessive type, mental retardation, multiple congenital anomalies.

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СИНДРОМ БАЗЕЛЬ-ВАНАГАЙТЕ-СМІРІНА-ЙОСЕФА

Синдром Базель-Ванагайте-Сміріна-Йосефа – рідкісний синдром генетичної розумової відсталості, зумовлений аутосомно-рецесивною мутацією гена MED 25. Проаналізовано 112 історій хвороби пацієнтів віком від 1 місяця до 3 років із судомами. За час спостереження виявлено симптоми, характерні для синдрому Базель-Ванагайте-Сміріна-Йосефа. Порівнюючи частоту клінічних симптомів у цього пацієнта з іншими, ми встановили, що для цього синдрому більшою мірою характерне поєднання рідких брів і волосся, широкого чола, ретрогнатії, гіпертелоризму з вадами розвитку головного мозку та серця, а для ранньої діагностики слід рекомендувати підхід, заснований на глибоких дослідженнях. Мультидисциплінарний підхід до лікування симптомів та своєчасна профілактика ускладнень можуть покращити якість життя цих пацієнтів.

Ключові слова: синдром Базель-Ванагайте-Сміріна-Йосефа (BVSYS), ген MED25, аутосомно-рецесивний тип, розумова відсталість, множинні вроджені аномалії.

Basel-Vanagaite-Smirin-Yosef syndrome is a rare genetic syndrome caused by an autosomal recessive mutation of the MED 25 gene (19q13.33) [1]. This syndrome is characterised by severe developmental delay, various craniofacial, neurological, cardiac and ocular abnormalities. Currently, this disease has been reported in only a few patients in the world. Since 2015, 20 patients with common clinical features and MED25 biallelic variants have been described through whole exome sequencing, leading to a better definition of the phenotype associated with BVSYS [2, 3].