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REACTION OF PERIPHERAL BLOOD LYMPHOCYTES OF ADOLESCENTS WITH DEPRESSION TO CHEMICAL MUTAGEN *IN VITRO*

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The study of chromosomal disorder incidence allows us to assess influence of environmental factors on human body that is due to the fact that the level of spontaneous chromosomal mutagenesis in human population is a relatively constant value used to assess susceptibility of human body to the effects of mutagenic agents. The purpose was assessment of reaction of peripheral blood lymphocytes of adolescents with depression to chemical mutagen in vitro. Cytogenetic analysis was carried out in 24 adolescents aged 14 to 18 of both sexes with depression. Spontaneous and induced level of chromosome aberrations in blood lymphocytes of patients in vitro was determined; latent chromosomal instability was calculated. Statistical data was processed using Excel software package using Student's t-test. Spontaneous level of chromosomal disorders in intact cultures of blood lymphocytes of adolescents with depression constituted 8.3 and it increased up to 17.5 per 100 metaphase plates after the effect of mitomycin C on blood lymphocytes of patients. Spontaneous individual frequency of chromosome aberrations in groups of girls and boys with depression did not differ and it increased significantly after the effect of chemical mutagen on blood lymphocytes in vitro of patients, mainly due to chromosome aberrations in boys. We determined the level of spontaneous and induced mutagenesis in blood lymphocytes of patients with depression in vitro, which was twice the spontaneous level of chromosome aberrations after mutagen introduction into the culture mixture that indicates pronounced individual and group latent chromosomal instability in adolescents with depression.

Key words: *adolescents, depression, mutagen, aberrations, chromosomal instability.*

Relationship of the publication with the planned research works. This research is a fragment of research "To Improve System of Medical and Social Rehabilitation of Adolescents with Depressive Disorders" (01.01.2022 to 31.12.2024), state registration № 0121U114418.

Introduction. In recent years in all countries of the world, including Ukraine, there has been an increase in frequency of depressive disorders among various segments of population, especially among the younger generation. Adolescent depressive disorders are characterized by significant destructive potential since they are life threatening [1, 2]. We know a number of factors (environmental, socio-demographic, genetic, immunological, endocrine factors, etc.) that influence formation of depressive disorder and explain pathophysiology of the disease which pathogenesis involves combination and connection of these factors. That is, the combined influence of environmental factors and hereditary factors that act through immunological and endocrine reactions initiates structural and functional changes in many areas of the brain. This, in turn, leads to dysfunctional neurogenesis and neurotransmission and further manifests itself as a set of symptoms that constitute depression [3]. As a result of interaction of these factors, adolescents may experience disorders that lead to shifts in the immune system, cause carcinogenesis development and life expectancy decrease. And it is the mutation incidence that reflects the intensity of changes in heredity that leads to formation of reproductive disorders, infertility, and birth of children with hereditary diseases [4]. High cell mutability in diseased organism is a sign of genome variation or instability and is manifested by an increase in the level of chromosome aberrations (ChA) in peripheral blood lymphocytes (PBL) [5]. Genome instability is a multistage process which includes the stages of preparation (endomutogenesis intensity increase and reduction of efficiency of genome protection systems), formation (genome damage with reduction of mutant cell elimination intensity that leads to transformation of primary DNA damage into visible displacements, causing impaired gene expression and occurrence of abnormal metabolites with mutagenic activity), and completion (endomutagen level in the body decreases and defense system activity normalizes) of this process [6, 7].

At the present stage, study of mutagenesis features is not limited to assessment of spontaneous level of chromosomal disorders, but includes determining the susceptibility of human somatic chromosomes to additional test mutagenic load *in vitro*. And it is the additional chemical effect of model mutagens (dimethoate, bleomycin, mitomycin C) used by many scientists to PBL that allows us to assess chromosome susceptibility *in vitro.* If somatic chromosome susceptibility increase is observed due to model mutagen effect, this indicates the existence of latent chromosomal instability (LCIN) [8]. In turn, LCIN plays an important role at cytogenetic level in genome destabilization, a phenomenon when multiple changes accumulate in cells over time causing transition of stable genome of normal cells to unstable genome which is common, in particular, for tumor cells [9]. Our previous studies revealed significant increase in spontaneous and induced level of chromosomal damage in children with depressive disorder [10, 11]. At the same time, it was necessary to study chromosomal instability in adolescents with depression because chromosomal apparatus destabilization at various pathologies can occur due to influence of various factors,

including emergencies, so it is extremely important to identify high-risk individuals before occurrence of high level of chromosomal disorders.

The purpose of the study. Assessment of reaction of peripheral blood lymphocytes of adolescents with depression to chemical mutagen *in vitro.*

Object and methods of research. Cytogenetic analysis was carried out in accordance with international requirements [12] in 24 adolescents (12 girls and 12 boys) aged 14 to 18 of both sexes with depression. Additional mutagenic effect of mitomycin C on PBL was used to determine possible latent chromosomal instability (LCIN) *in vitro*. Mitomycin C is a cytostatic drug belonging to the group of antitumor antibiotics that inhibits DNA synthesis and, at high concentrations, RNA and protein synthesis. The most active mitomycin C in the late G_1- and S-phases of mitosis can induce significant amount of chromosomal damage at non-toxic dose levels.

Preparations of metaphase chromosomes were encrypted and analyzed using blind study method in binocular microscope *Leica CME* (Austria), 10x18 eyepiece, 100x lens, 1.25x binocular adjustment. 100 metaphase plates were analyzed in each patient. We analyzed 4400 metaphase plates of which 2200 metaphases before mitomycin C effect on blood lymphocytes and 2200 – after the effect. We calculated such indicators as the total incidence of chromosome aberrations (per 100 metaphases analyzed), incidence of certain types of chromosome aberrations (per 100 metaphases analyzed), and latent chromosomal instability.

In order to identify individuals with hypersusceptibility to the effect of mitomycin C, the coefficient of latent chromosomal instability (C_{LCIN}) was calculated as follows:

$$C_{LCIN} = M_{LCIN}/M,$$

where M_{LCIN} – individual values of chromosome aberration incidence during the test effect of mitomycin C at the concentration of 3 μg/ml; M – mean group values of chromosome aberration incidence at the concentration of 3 μg/ml. For individuals with hypersusceptibility, the induced cytogenetic effect will always exceed the mean group level of chromosome aberrations, so their C_{LCIN} will exceed 1.

Statistical processing of obtained data was carried out using *Excel* software package. Student's t-test [13] was used to determine the probability of differences between groups.

When examining adolescents with depression, we observed the principles of the Declaration of Helsinki, the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, and the relevant laws of Ukraine. We obtained informed consent of parents and patients aged 14 and above to participation in cytogenetic research. Research protocol was approved by the Institute's Local Bioethics and Deontology Committee for Surveyed Adolescents.

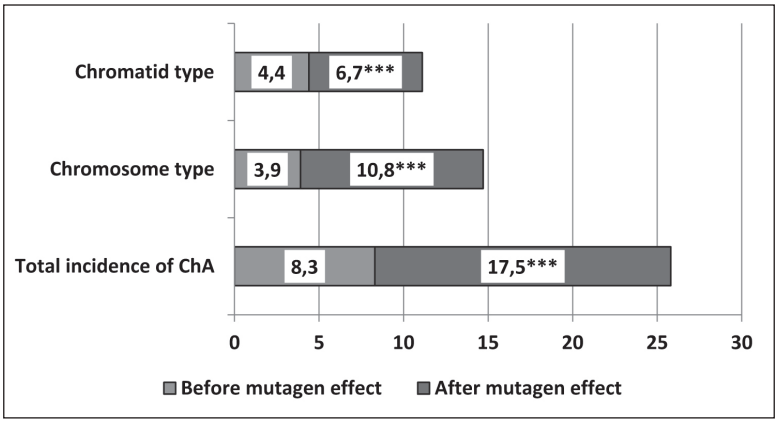

Figure 1 – Level of Chromosome Aberrations in Intact and Mitomycin C-induced Blood Lymphocytes of Patients with Depression (%).

Note: *** – significance of differences p=0.001.

Research results and their discussion. Having assessed the level of chromosomal instability in PBL of sick adolescents, we determined that all patients had various structural chromosome disorders both before and after the effect of mitomycin C on PBL. The spontaneous level of chromosomal disorders in intact cultures of adolescents with depression constituted 8.3 per 100 metaphase plates and it doubled after the effect of mitomycin C (up to 17.5 per 100 metaphase plates) **(fig. 1)**.

Frequency of aberrations of chromatid type increased 1.5 times, chromosome type – 2.6 times. Both before and after mutagen effect on PBL of patients, single acentric fragments prevailed among chromatid type aberrations and paired acentric fragments and dicentric chromosomes prevailed among chromosome type aberrations **(table 1)**.

Analysis of individual incidence of blood lymphocyte susceptibility in patients with depression to classtogenic effect of chemical mutagen showed that the level of chromosome aberrations before the effects of mitomycin C *in vitro* was 3.0 to 21.0 per 100 cells and after mutagenic load – 9.0 to 23.0 per 100 cells **(fig. 2)**.

It is known that not all individuals have a relationship between individual values of spontaneous mutagenesis and individual radiosensitivity value of BLP *in vitro* [14]. Among the examined adolescents with depression, only 8.3% of patients (2/24) with high level of spontaneous mutagenesis (11.0 and 9.0 per 100 cells) did not have high blood lymphocyte susceptibility to the effect of mutagen *in vitro* (9.0; 9.0 per 100 cells) that may indicate the existence of genotypes which contribute to and are protective to effects of various mutagens.

Considering high level of chromosomal damage in patients' blood lymphocytes, we examined the coef-

Table 1 – Frequency of Chromosome Aberrations in Blood Lymphocytes of Adolescents with Depression (n=24) before and after Mutagenic Load by Mitomycin C on PBL

Aberration type	Before Mutagen		After Mutagen	
	Number of Chromosome Aberrations			
	n=2400		n=2400	
	n (abs.)	M±m (%)	n (abs.)	M±m (%)
single acentric fragments	106	4.4±0.4***	160	6.7±0.5***
paired acentric fragments	87	3.6±0.4***	218	9.1±0.6***
dicentric chromosomes	6	0.25±0.1***	33	1.4±0.2***
chromatid-isochromatid interchanges	2	0.08±0.06	8	0.3±0.1

Note: Significance of differences: *** – p=0.001

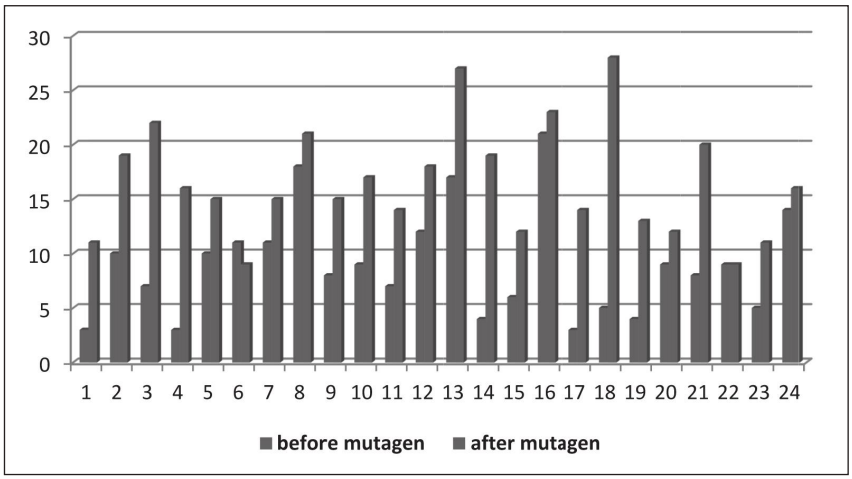

Figure 2 – Taking the path of taking the path of taking the path of Individual Incidence of Blood Lymphocyte Susceptibility in Patients with Depression to Classtogenic Effect of Chemical Mutagen (%).

Table 2 – Comparative Analysis of Incidence of Various Chromosome Aberration Types in Boys and Girls with Depression, M±m (%)

Aberration type per 100 cells		Patients with depression			
		boys (n=12)		girls (n=12)	
		Number of Chromosome Aberrations			
		n=1200		n=1200	
		before mutagen	after mutagen	before mutagen	after mutagen
Chromatid type	single acentric fragments	4.7±0.6	6.8±0.7	4.2±0.6	6.5±0.7
Chromosome type	paired acentric fragments	3.8±0.5	11.1±0.9***	3.5±0.5	7.1±0.7***
	dicentric chromosomes	0.3±0.1	0.8±0.3**	0.3±0.1	1.9±0.3**
	chromatid-isochromatid interchanges	0.08±0.08	0.3±0.1	0.08±0.08	0.4±0.1

Note: Significance of differences: *** – p=0.001

ficient of latent chromosomal instability (C_{LCIN}) for individuals with hypersusceptibility. We found that the cytogenetic effect induced by mitomycin C exceeds mean group level of chromosomal aberrations and corresponds to > 1 in 46.0% of patients and the coefficient of latent chromosomal instability was less than one in 54.0% of patients. Thus, significant increase in both total and individual levels of ChA in blood lymphocytes of 22 out of 24 adolescent patients was recorded after application of testing mutagenic load to BLP. In other words, individual somatic chromosome susceptibility to additional mutagenic load *in vitro* did not depend on sex and influence of mutagenic environmental factors and is genetically determined [15].

The number of aberrations before the effect of mitomycin C on blood lymphocytes of sick boys (8.8 per 100 metaphases) and girls was almost identical (9.1 per 100 metaphases). Individual values varied within the range of 3.0 to 18.0 in girls and 4.0 to 23.0 per 100 metaphase plates in boys. Chromatid and chromosome aberrations were determined in both groups of adolescents examined **(table 2)**.

It is beyond argument that one of the valid reasons of genome destabilization is changes in maintaining the genome stability, i.e., a whole group of RNA-editing proteins AID/APOBEC that inhibit expansion of retroelements which can cause formation of mental disorders.

Considering the data obtained, specialists face the question of monitoring the state of chromosomal apparatus in adolescents with depression because cells containing chromosome disorders have high probability of oncogenic transformation or causing infertility in adulthood.

Conclusions. We determined the level of spontaneous and induced mutagenesis in blood lymphocytes of patients with depression *in vitro*, which was twice the level of chromosome aberrations after mutagen introduction into the culture mixture that indicates pronounced individual and group latent chromosomal instability in patients with depression.

Prospects for further research. Involve study of chromosomal instability in blood lymphocytes of patients with depression depending on the therapy used.

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РЕАКЦІЯ ЛІМФОЦИТІВ ПЕРИФЕРИЧНОЇ КРОВІ ПІДЛІТКІВ ІЗ ДЕПРЕСІЄЮ НА МУТАГЕН-ПРОВОКАТОР *IN VITRO*

Багацька Н. В.

Резюме. Дослідження частоти хромосомних порушень дозволяє оцінити вплив чинників навколишнього середовища на організм, що обумовлено тим, що рівень спонтанного хромосомного мутагенезу в популяції людини є відносно сталою величиною, яка використовується для оцінки чутливості організму до дії мутагенних факторів.

Цитогенетичний аналіз проведено згідно міжнародних вимог у 24 підлітків (12 дівчат і 12 хлопців) 14-18 років обох статей із депресією. Для визначення можливої прихованої хромосомної нестабільності використовували додатковий мутагенний вплив мітоміцином С на лімфоцити крові *in vitro*. Статистична обробка отриманих даних здійснювалася з використанням пакету програм *Excel*. Для визначення вірогідності відмінностей між групами застосовували критерій Стьюдента.

Спонтанний рівень хромосомних порушень в інтактних культурах лімфоцитів крові підлітків з депресією становив 8,3, а після впливу мітоміцину С на лімфоцити крові хворих він зростав до 17,5 на 100 метафазних пластинок. Частота аберацій хроматидного типу збільшилася у 1,5 рази, хромосомного типу – в 2,6 разів. Як до впливу мутагена на лімфоцити крові хворих, так і після серед аберацій хроматидного типу переважали одиночні ацентричні фрагменти, серед аберацій хромосомного типу – парні ацентричні фрагменти та дицентричні хромосоми.

Спонтанна індивідуальна частота аберацій хромосом в групах дівчат і хлопців із депресією не розрізнялася, а після впливу мутагена-провокатору на лімфоцити крові *in vitro* хворих достовірно збільшувалася, причому переважно за рахунок аберацій хромосомного типу у хлопців. Цитогенетичний ефект, індукований мітоміцином С, у 46,0% хворих перевищує середньогруповий рівень хромосомних аберацій і відповідає > 1; а у 54,0% хворих коефіцієнт прихованої хромосомної нестабільності був менше одиниці. Отже індивідуальна чутливість хромосом соматичних клітин до додаткового мутагенного навантаження *in vitro* не залежала від статі та впливу мутагенних факторів середовища і є генетично детермінованою.

Визначено рівень спонтанного та індукованого мутагенезу в лімфоцитах крові хворих з депресією *in vitro*, який вдвічі перевищував спонтанний рівень хромосомних аберацій після внесення мутагена в культуральну суміш, що вказує на виражену індивідуальну та групову приховану хромосомну нестабільність у підлітків із депресією.

Ключові слова: підлітки, депресія, мутаген, аберації, хромосомна нестабільність.

REACTION OF PERIPHERAL BLOOD LYMPHOCYTES OF ADOLESCENTS WITH DEPRESSION TO CHEMICAL MUTAGEN *IN VITRO*

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Key words: adolescents, depression, mutagen, aberrations, chromosomal instability.

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Zagoruyko G. E., Martsinovsky V. P., Husakovska T. M., *Filatova V. L., Zagoruyko Yu. V.

KINETICS OF THE DEVELOPMENT OF THE MICROCIRCULATORY TRACT OF THE MYOCARDIAL COMPLEX (LV + IVS) IN THE PROCESS OF EARLY POSTNATAL ONTOGENESIS OF RATS WISTAR

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Determination of the kinetics of the development of the microcirculatory bed (MCB) of the mammalian myocardium remains an urgent problem of ontogenesis. The work aimed to study the regularities of the volume ratios of the capillary (cap) and arteriolo-venular (a+v) components in the process of postnatal development of the myocardial MCB in the complex "left ventricle + interventricular membrane" (LV+LV) of the heart of Wistar rats. Electron-microscopic, optical and morphometric analysis of the ultrastructures of the MCB of the myocardium of rats from birth (d/b) to 45 days was carried out. The following morphometric parameters were determined: 1- relative volumes (%): Vvmcb, Vvcap, Vv(a+v) = (Vvmcb–Vvcap); 2 – absolute volumes (μm3): Vmcb, Vcap, V(a+v) = (Vmcb–Vcap); 3 – average daily growth rate (μm3/day): vcap/day; v(a+v)/day. It was established that after the birth of rats, the morphological processes of intensive growth of the volumes of the components of the blood microcirculatory channel occur in the myocardium (LV+IVS). In newborns and 5-day-old rat pups, numerous blood microvessels were found, the endotheliocytes of which were in the process of proliferation and differentiation. The obtained results of the conducted morphometric analysis of myocardial negatives indicated that on the 10th day after the birth of the animals, the maximum average daily growth rate of the volume of the capillary component (vcap) was determined in the MCB of the myocardium, and on the 25th day – the maximum average daily growth rate of the arteriole volume -venular component- v(a+v). In the myocardium of newborn rats, the ratio of volumes (a+v)/cap was equal to 1 : 44. At t → 45 days, there was a significant increase in the ratio of volumes v(a+v)/vcap to 1 : 3.1 as a result of absolute growth volume of microvessels (a + v). In the process of postnatal angiogenesis, the source of the formation of arterioles and venules in the blood-carrying MCB of the myocardium (LV+IVS) is the existing capillaries.

Key words: *angiogenesis, morphometry, capillaries, arterioles, venules.*

Connection of the publication with planned research works. The work was carried out by the theme of the SRW: "Anatomical and physiological aspects of growth and development of humans and animals." State registration number 0116U002990.

Introduction. Over the past 20 years, numerous works by cardiologists, pathomorphologists, clinicians, and physiologists have been devoted to studying angiogenesis and biological functions of the MCB of the myocardium of humans and laboratory animals [1-4]. This is because almost all heart diseases are associated with disorders of metabolic processes in cardiomyocytes (CMC) and components of the MCB of the myocardium [5-8]. Arterioles, capillaries, venules and arteriolo-venular anastomoses are distinguished as part of the blood microcirculatory channel of the myocardium [1, 2, 5]. Currently, the capillary link of the MCB, which performs the functions of transport and transmembrane move-