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## OPTIMIZATION OF PHYSICAL EDUCATION IN HIGHER EDUCATIONAL INSTITUTIONS THROUGH THE PRISM OF TECHNOLOGIES OF PEDAGOGICAL PROCESS OF TEACHING DISCIPLINE

**Abstract. Abstract.** *Based on the task analysis subsystem physical training, psychological structure of future trade issue highlights the nature and criteria optimization teaching physical education students. It was established that the essence of fitness lies: to change the organization of training by introducing technologizing in this process; a more precise definition directly to specific goals in terms of implementing practical purpose of learning; in the exercise of personal-active approach. Optimization criteria are: efficiency and quality of educational decisions and educational tasks; justified expenses necessary time and effort to achieve the intended results.*

**Keywords:** *optimization, student, physical training, technologization*

### Introduction.

The training of a future specialist is a multifaceted learning process that includes a number of types of training (theoretical, psychophysiological, physical, and others). Focusing the results of pedagogical influences on all types of training and determining professional readiness. Today, an active search for new forms and methods of physical education is taking place, which would help to improve the quality of training of future specialists in higher educational institutions. However, the analysis of special literature [3, p.5] shows that the methods used in the organization of physical education in higher education institutions are not sufficiently effective to ensure the proper level of physical fitness of students. In recent years, the methodology of conducting training in higher education institutions has not changed particularly, its effectiveness is relatively low, which does not meet the modern requirements of higher education [6, p.7]. Today, the issue of intensifying the work of specialists is sharp, the requirements for the quality of training specialists in higher educational establishments, the specific types of professional activity are increasing, and, accordingly, there is a need for profiling of physical education, taking into account the requirements of the chosen profession. Existing programs are limited to general recommendations without specific models of

modes of development of general and special professional qualities. As a result, the majority of graduates of higher educational institutions are not able to work qualitatively with the efficiency that modern production requires [2, p.6]. Educational reform requires consideration of this problem from the standpoint of modern technologies for improving the quality of education in accordance with the new state educational standards.

**The analysis of recent studies and publications** indicates that the optimization of the pedagogical process remains a factor that intensifies the pedagogical process, increases its efficiency in each unit of time.

**The purpose of the work:** to study the features of the modern organization of physical education in universities and give an analysis of optimization of the educational process on the physical training of students in the period of study.

**Presentation of the main research material with full justification of the scientific results obtained.** The main problem of the professional formation of a specialist in higher education, one of the most important directions of intensification of the psychological and pedagogical process of preparation was and remains to find ways to optimize the ratio of results and costs of human activity, which in general is called efficiency. The concept of "pedagogical system of training future specialists" is understood as "a complex of

effective means, specific procedural principles, content, methods and techniques for the formation of professionally meaningful qualities, methods and criteria for assessing professional readiness, the functioning of which is determined by the objectives of professional training and the principles of designing process models that focus interdisciplinary connections and attitudes in solving pedagogical tasks of such preparation "[4]. Physical education in higher educational institutions, as a component of the educational system of training, is understood as a specially organized and guided pedagogical process, aimed at teaching motor activity, development of physical qualities of students. Physical education combined with ethical, aesthetic and intellectual acquires importance of one of the main factors of the comprehensive development of the person.

The tasks of physical education in universities are: formation of the basics of theoretical knowledge, practical and methodical abilities (skills and abilities) in the student's youth from physical education and sports education, physical rehabilitation, mass sports as components of their full, harmonious and safe life; Student youth experience in the use of acquired values during life in personal, educational and professional activities, in everyday life and in the family; Provide students with the appropriate level of development of indicators of their functional and morphological capabilities of the body, physical qualities, motor abilities, disability; promoting the development of professional, ideological and civic qualities of students; preparation and participation of students in various sporting events. The recommendations of the Bologna Declaration provide for the reform of higher education through optimization of the educational process, which involves the functioning of the pedagogical process from the point of view of the given criteria on the basis of the full consideration of the principles, modern forms and methods of education, education, as well as the personal and collective features of a particular group.

Introduction to the scientific circle of the concept of "optimization" is associated with the emergence of the need to improve the forms and methods of organization of educational activities.

The term "optimization" goes back to the verb "to optimize" through the adjective "optimal", first recorded in private dictionaries in our country

and abroad in the early 60's of the twentieth century, and is interpreted as "compiling, calculating the program, the most acceptable model of organization of what Anything ». As a word of Latin origin, "optimization" is defined as the choice of the best (optimal) variant of the problem from the set of possible under these conditions [3].

According to many scholars, the optimization of the pedagogical process of physical training, which is based on new technologies, includes the following structural components: learning objectives and diagnostic objectives of the planned learning outcomes; content of training; means of diagnostics and control of the status of learning outcomes; teaching methods; organization of educational process; learning means; the result of activity - the level of achievement of general education and professional training.

The essences of the process of optimizing the training of students during physical training are:

- changing the organization of training itself by introducing technology in this process;

- to more precisely define the immediate specific goals in the realization of the practical purpose of training;

- in the implementation of personality-activity approach.

- Criteria for optimization in the process of physical training of students may be:

- efficiency and quality of educational-educational tasks solution taking into account the professional orientation of physical training;

- The expenses of the time of students and teachers for the achievement of the planned results must be justified;

- The cost of the efforts of students and teachers to achieve the intended results over time is affordable.

The analysis of the above studies shows that the definition of pedagogical technology as a coherent interrelated system of actions of a teacher and a student is sufficiently complex, which is connected with the application in the pedagogical process of a set of methods of education and training for solving various pedagogical tasks.

It has been established that technology is possible through the creation of new vocational training systems that are oriented towards the adaptation of well-known pedagogical

technologies.

Therefore, they must be transformed according to the particulars of the subject of study.

Based on the analysis of existing approaches to the definition of the structure of pedagogical technologies, we consider the following structure to be the most optimal: the conceptual basis, the content and procedural part of the training. The content of the training should determine the general and specific purpose of training, the content of the training material. In the procedural part it is necessary to describe: organization of educational process, methods and forms of educational work of students, methods and forms of work of the teacher, activity of the teacher on the process of mastering the material, diagnostics of the educational process.

Conceptual component of pedagogical technology includes philosophical, psychological, didactic and socio-pedagogical substantiation of achievement of educational goals. In accordance with the principle of orientation to innovation, the educational process in a higher educational institution should be aimed at the introduction of scientifically grounded and experimentally tested the latest pedagogical technology.

Summarizing the proposed innovative training models [7], the authors believe that in the field of higher education the most relevant innovations are:

- reorientation of the purpose of physical training to obtain the ability to use the means of AF to increase the effectiveness of training in mastering their skills of their future specialty, aimed at the development of the individual, his ability to scientific, technical and innovative activities on the basis of social order; designing the educational process as a system that promotes self-development of the individual;

- restoration of the content of the training, which implies: the exclusion from the programs of the material, which is only descriptive; integration of knowledge acquired during the study of related disciplines; preconditions created for problem-module study of a number of disciplines; conducting optional innovative and experimental work;

- shifting the focus from the process of teaching to the learning process of the students themselves, mastering them the experience of self-education under the leadership of the teacher

on the basis of increasing non-auditing independent work by reducing the audience, building the latter to a reasonable minimum, which will allow students to free time for independent training, and will enable them work at their own pace and according to their interests;

- providing the educational process with material and technical means at the level of modern socio-cultural development of society.

Conclusions from this study and prospects for further exploration in this direction. The most important tasks of the subsystem of physical training are: firstly - increasing the effectiveness of training future professionals in mastering their skills in their specialty; and secondly, systematic improvement and maintenance of the qualities most important for the future profession.

The essence of the pedagogical process of optimizing the physical training of undergraduate students is to: change the organization of learning itself by introducing technology in this process; in a more precise definition of immediate specific goals in the realization of the practical purpose of learning; in the implementation of personality-activity approach.

The criteria for optimization in the process of physical training of students can be: efficiency and quality of the solution of educational and educational tasks, taking into account the professional orientation of special physical training; The costs of the efforts of students and faculty towards reaching the intended results over time are available.

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## PECULIARITIES OF THINKING OF THE CHILDREN OF THE ELDERLY PRESCHOOL AGE WITH DISORDERS OF INTELLECTUAL DEVELOPMENT

**Abstract.** *The article found that the thinking of a senior preschooler with intellectual disabilities has the following features: disorders of all mental operations(to a greater extent abstraction, generalization); decrease in activity of thought processes, not activity in search of the solution, indifference o the result and process of the solving even the game problem; speech development; thinking is formed in conditions of defective sensory cognition; limited practical activity; the most preserved kind of thinking - demonstrably effective The dependence of the peculiarities of behavior of children with intellectual disabilities on the reasons that caused it is analyzed. Basic psychic properties of older preschool children are characterized. It is proved that such basic mental properties as creativity, initiative, independence and responsibility, arbitrariness, freedom of behavior and safety, self-awareness and self-esteem, which are characteristic for a preschooler with normal mental development, are not formed in a child with a mental disability. The cognitive processes are slowed down: memory, perception, thinking, poorly developed speech, there is a significant underdevelopment of motor skills.*

**Keywords:** *preschool child, thinking, intellectual disabilities, intellectual defect, correctional education and upbringing of children with intellectual disabilities*

**Introduction.** At the present stage of development of psychological and pedagogical science, social changes in our Ukrainian state, the need for rethinking society's attitude to the problems of childhood is actualized. Child-centrism is a priority direction and principle of Ukrainian educational policy. It is precisely the respect for needs of the child, the recognition of the value and the importance of preschool childhood that can ensure our country's entry into the European Educational Society, effectively influencing the European integration processes.

Attitude towards childhood is an indicator of a country's civilization, level of development and potential. In these conditions, the problems of inclusive education are especially acute, because in the opinion of Ionin L. "Society should give any person the right to choose the type of education depending on his interests, needs, opportunities; the breadth of education provision should be ensured" [4, 31].

Today, the focus is on "... the development of methodological and theoretical foundations for the introduction of innovative educational programs and technologies, focused on the qualitative improvement of the process of socialization of persons with disabilities. Integrated (inclusive) education - the process of

joint education of ordinary and atypical children, establishment of closer relationships in the process of their upbringing in a collective of the collective school, is the most priority and natural direction of this work [5].

In this perspective, it is impossible to increase the value and importance of preschool childhood, which should be as complete and harmonious as possible for children with special educational needs, for children with intellectual disabilities. "... Childhood is a period of birth and formation of a person with his or her future spiritual and moral values, a period of knowledge of the society and its majesty of man; the discovery by the child of the realm of Life on the Earth in all its diversity.

With all its positive and negative manifestations; these are the first steps of learning; it is the thirst for knowledge, these are the first joys, the first disappointments and the first tears... It is finally the foundation of becoming a citizen and a patriot of one's Crane" – says Academician A. Bogush.

This also applies to preschool children with intellectual disabilities. Early diagnosis of deviations in mental development during preschool childhood offers many potential opportunities for preventing intellectual

disabilities and organizing complex corrective psychological, medical and pedagogical rehabilitation work, which will contribute to the most adequate social adaptation and integration of such children into society.

Consequently, correctional education and upbringing for children with intellectual disabilities should begin with a restructuring of the outlook on preschool childhood, on integrated education that is still resilient in societies and among modern fatherhood.

**The purpose of the study** is to outline the psychological and behavioral characteristics of children with intellectual disabilities, to characterize thinking as a reflection of the subjective reality of the individual; to compare basic mental properties of preschool children with intellectual disabilities and normal children.

**Material and Methods** were used to ensure the validity of the provisions and conclusions, and to solve the tasks of the work, which correspond to the content of the problem and the stages of its study. Theoretical and methodological analysis of literary sources in order to determine theoretical approaches to the interpretation of the content, types and manifestations of thinking features in children with intellectual disabilities; deductive - for the systematic description of the phenomenon under study, inductive - for establishing the behavior of children with intellectual disabilities; logical-semantic - to deepen and clarify the concept of "characterization of basic mental properties of children of preschool age" children with intellectual disabilities.

**Research results.** Before considering the psychological characteristics of children with intellectual disabilities, let us dwell on the psychological characteristic of thinking as a reflection of the subjective reality of the individual. Thinking, according to many scientists (L. Stolyorenko, S. Samigin, V. Stolyorenko), is the most generalized and indirect form of mental reflection that establishes connections and relationships between objects that are known.

The main functions of thinking are to expand the boundaries of knowledge through sensory perception. Thinking as a scientific definition is very diverse in the scientific thesaurus. In Jung's typological model, thinking is one of the basic functions used for psychological

orientation[8].

The task of thinking about uncovering objects, identifying them and separating them from random coincidences. Thinking operates on concepts and assumes the functions of generalization and planning [7, 23]

Therefore, thinking is a cognitive process, the development of a person's creative abilities, which are formed and developed in the course of work. Thinking unfolds as a process of solving problems of varying complexity, in which there are conditions and requirements where motives and emotions play an important role. In modern psychological and pedagogical sciences, thinking is studied in the context of interpersonal relationships of people, their upbringing and learning.

The main criteria for thinking scientists believe the following: problem (ability to find difficulties and ways to solve them); systematic (ability to take into account the causes that affect the outcome); anticipation (the ability to anticipate the consequences of their decisions); professionalism (ability to actively use their professional knowledge); flexibility (ability to use the opposite viewpoint); analyticity (ability to distinguish opinions from facts); non-inertia (ability to make decisions regardless of experience and knowledge); promptness (ability to respond quickly to changing circumstances); methodical (ability to consistently, without distraction from the goal, to understand the situation) [5, 133].

The development of thinking of a child of preschool age occurs gradually, during its subject activity and communication, learning of social experience. Visual-effective, visual-figurative and verbal-logical thinking are consecutive steps of a child's intellectual development. According to L. Stolyarenko, "Generally developed means of using objects are the first knowledge (generalizations) that a child learns through adult and social experience" [10, 124].

*Visual-effective thinking* is a type of thinking that relies on the direct perception of objects, a real transformation in the process of action with objects. *Visual-figurative thinking* - a type of thinking characterized by reliance on imagination and images; the functions of visual thinking are related to a specific situation and changes in it that a person wants to gain as a result of his

activities. Great influence on the development of thinking has speech. *Visual-active thinking* is the earliest form of thinking that occurs in a child in the first, second year of life, even before the development of the baby's speech. The child enters into practical communication with other people, especially with his relatives.

At the stage of *visual thinking* is the first elementary child on the basis of emotionally vivid particularities that are dominant in the child's attention. Associations are involved in generalizations of this type. Visual thinking is clearly manifested in preschoolers 4-6 years old, and visual thinking is retained, but is no longer crucial, the connection between thinking and practical actions is not as close to direct and immediate as it was before. Therefore, a senior preschooler with normal intellectual development thinks only through visual images and does not yet have concepts. Scientists distinguish between two stages of thinking: pre-conceptual and conceptual. In pre-school the thinking differs from that of an adult and is in the pre-stage. The child's judgments are individual and relate only to a specific subject. Most of the judgments, according to scientists [10], are judgments of similarity, or judgments by analogy, because memory plays a major role at this stage.

A specific feature of thinking of a child of preschool age is self-centeredness. A child under five cannot look at themselves, cannot properly understand situations that do not match their point of view. Features of child logic, according to self-centeredness, are the following: *insensitivity to contradictions*; *syncretism* (the tendency to associate everything with everything); *transduction* (transition from partial to partial, bypassing the common); *partial to partial, bypassing the common*; Lack of ideas about how to save quantity. Under the condition of normal intellectual development, there is a pattern - there is a replacement of pre-(abstract) thinking (components - concepts, formal operations). Consequently, the child's thinking evolves from concrete images to perfect word-designated concepts. As for the thinking of children with intellectual disabilities, we are of the conceptual thinking (specific images), conceptual opinion of the supporters of high-quality scientific direction in the field of studying mental retardation.

The presented patterns and principles of development are the basis of our further analysis of the characteristics of mental and mental development of older preschoolers with impaired intellectual development. In our study, we (in accordance with the subject of the study) focus our attention on older preschoolers with mild mental retardation (obesity). Because: 1). This is the largest group of children that will influence the number of sample population in the future; 2). In the absence of additional disorders and from early, adequate organization of corrective and developmental measures, it is possible to achieve very positive shifts in thinking and developing the social skills of such children.

**Discussion.** To correct the thinking of children with intellectual disabilities, it is very important to analyze and know the reasons that led to this underdevelopment. Based on the analysis of the works of practical psychologists (A. Obukhivska, T. Ilyashenko, T. Zhuk) dealing with this problem, we have analyzed the reasons that influence the degree of mental retardation and peculiarities of behavior of such children. For clarity and structure of analysis, we give the presented factors in Table 1.1

Thus, the thinking problems of such children are primarily due to the properties of their nervous system and the nature of the causes that caused the underdevelopment of the intellectual sphere. The weakness of the cerebral cortex functions causes the slow rate of formation and the weakness of new neural connections. As a result, the problems of the thinking process. According to modern scholars for the thinking of children with intellectual disabilities are characterized by the following features:

- violation of all mental operations (to a greater extent abstraction, generation);
- reduction of activity of thought processes, inactivity in search of the solution, indifference to the result and process of solving even the game problem;
- speech underdevelopment
- thinking is formed in conditions of defective sensory cognition;
- limited practical activity;
- the most preserved kind of thinking - visual and effective;

Table 1.1

**Features of behavior of children with intellectual disabilities for the reasons that caused it**

Causes of intellectual development disorders	Features of behavior of children with intellectual disabilities
1. Brain injury	The intellectual defect is not significant. Extremely fast fatigue, unstable attention, forgetfulness and difficulty remembering. Low ability to absorb and accumulate knowledge and intellectual tension, from where - the desire to avoid this tension. Such children are difficult to bring up. They can, through fatigue, become irritable, unrestrained not find means of communication with adults and peers.
2. Encephalitis	There are various pathological changes in emotional and regulatory functions. Children who have had this disease are very irritable and inflammatory, hyperactive, and have an unstable mood. The stimuli respond very actively and quickly. However, they have a slow pace of thinking, high suggestion. In some cases, children may exhibit slow motion, sluggish monotony, poor speech.
3. Epilepsy	Slow course of all mental processes: slowly perceive educational material, speak, think very slowly, inertia of mental activity, It is very difficult to switch to another type of activity, which is caused by impaired mobility of the main nervous processes_ excitation and inhibition.
4. Schizophrenia	Autistic traits, unproductive thinking and fantasizing. Such children are poorly oriented in space and time. Reduced ability to generalize and abstract. Vocabulary poverty, a penchant for new meaningless word-formation. Emotional bluntness is manifested in the detachment from the environment, closeness, avoidance of contact, negativism.

process of solving problems;

- not critical thinking;
- weak regulatory role of thinking
- low motivation of mental activity;
- significant lag in the pace of development;

poorly oriented in space, unable to evaluate the properties of objects and the relationship between them;

- specificity and situational thinking;
- weakness of generalizations;

there is no possibility of solving visual problems [3, 145].

A thorough characterization of thinking is given by Academician V. Sinyov. He believes that the slowness and inertia of the course of the nervous processes determines the low productivity and stiffness of cognitive activity of children with intellectual disabilities [8, 193]. An interesting pattern is emphasized by all the researchers who dealt with this problem (V. Sinyov, N. Morozova, G. Dulnev, B. Pinsky) - a child with a disorder intellectual development quickly gets tired of work that requires intellectual effort, and

vice versa, for a long time can perform uninteresting, monotonous tasks without the involvement of intellectual effort. Such a child is often unable to find a rational solution to the problem, because her thinking is characterized by stiffness. The specificity and situationality of thinking is manifested in the fact that the child can distinguish only those properties of objects and phenomena, which he can feel in a certain way.

Reduced critical thinking causes the preschooler not to notice mistakes. Cognitive interests are not formed, for children with intellectual disabilities are characterized by psychic passivity, which is reflected in the rare adults with questions. As you know, the operational aspect of thinking is represented by the following operations: analysis, synthesis, comparison, generalization, abstraction. Describe these operations in a child with intellectual disabilities.

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Analysis as an operation of thinking is the separation of the constituents, features and properties of objects that are characterized by poverty, inconsistency in mentally retarded children, essential features are confused with minor ones. Synthesis is known to be an inverse analysis operation, too. A child with intellectual disability may have an incomplete, inaccurate understanding of the subject and may not properly combine the characteristics of the subject. Based on the operations of analysis and synthesis, the operation of comparison (the separation of common and distinguishing features of objects and phenomena). This operation is given with great difficulty to children with intellectual disabilities.

They can not form the criteria of comparison, distinguish a small number of differences between similar objects and phenomena, similarity is accepted for identity. As V. Sinyov emphasizes, it is easier for such children to identify signs of difference than signs of similarity. All analyzed operations of children with intellectual disabilities (analysis, synthesis, comparison) are chaotic. But children with intellectual disabilities suffer the most, such as operations such as abstracting (separating the essential properties of an object in a particular situation while separating them from insignificant ones) and generalizing them (combining objects and phenomena with essential common features into one category)).

The research of these operations was given considerable attention by N. Stadnenko in his works that there are 4 levels of generation in children with intellectual of generalization in children disabilities (zero; situational; generalization-grouping; conceptual generalization). The limits of our study do not allow us to describe these levels in detail They are quite fully represented in the scientific and pedagogical literature [8, 200]. We only emphasize that the children of this category have all the levels of generalization described.

It depends on the age of the child, their experience, the severity of the violation of intelligence. V. Sinyov emphasizes that "... a child who has conceptual generalizations, when complicating a task," slides "into a more primitive situation. Thus, all these levels of generalization can be observed in one child, but in different situations" [8, 200]. Thus, the analysis of scientific works (V. Sinyov, L.

Zankov, N. Stadnenko, N. Morozova, G. Dulnev, B. Pinsky) on the presented problem leads to the conclusion that vagueness, the indifference of concepts, the inability to go beyond direct concrete experience.

The theoretical analysis of the development of older preschoolers with intellectual disabilities was carried out within the framework of a systematic approach and included characteristics not only of the thinking but also of the mental properties of such a child. The basic characteristics of a preschooler (A. Bogush) are such mental properties as: creativity, initiative, independence and responsibility, arbitrariness, freedom of behavior and safety, self-awareness and self-esteem. Let's try to analyze the characteristic properties and the degree of their development of a preschool child with normal development and a child with intellectual disability.

The result of the comparative characteristics are presented in table 1.2.

Comparison of the characteristics of basic mental properties of older preschool children in normal and intellectual disabilities shows that the mental development of such children are very complicated without corrective education. The main thing - in a child with intellectual disability, all mental processes occur very slowly, without active motivation to any activity, to the environment, to social phenomena; the researchers emphasize the passive attitude of such preschoolers to their peers to adults, to themselves.

Such basic mental properties as creativity, initiative, autonomy and responsibility, arbitrariness, freedom of behavior and safety, self-awareness and self-esteem, which are characteristic of a preschooler with normal mental development, are not formed in a child with a mental disability. The cognitive processes

Table 1.2.

## Comparative characteristics of basic mental properties of preschool children

Mental properties	Characterization of mental properties in children is normal	Characterization of mental properties in children with intellectual disabilities
Creativity	Ability of the child to creatively solve any problems that arise in various life and educational situations; the ability to create a new original product.	The decrease in the rate of development of perception, the formation of perceptual actions only begins, which significantly complicates the formation of creativity, without special training productive activity is not formed.
Initiative	Indicators of the development of the creative intelligence of the child, manifested in play, productive, artistic and speech activity	Inhibited initiative, passive perception of reality, lack of cognitive motives. By the end of preschool age, the main activity is not game, but subject. The game has a stereotype, formality of action. Broadcasting is detached from activity. The passive dictionary far exceeds the active one
Independence and responsibility	A peculiar form of child activity that reflects the actual level of personality development (L. Vygotsky)	Inhabited autonomy, first of all self-care skills are formed, subject actions are characterized by lack of formability and imperfection
Randomness	Ability to manage their behavior in accordance with the requirements, rules, norms of behavior (L. Vygotsky, O.Zaporozhets)	They have difficulties in regulating behavior, overcoming obstacles, completing a case, there is no need to manage their behavior
Freedom of conduct and security	Caution, predictability, sense of security, sense of security, observance of socially-determined rules and prohibitions	Involuntary, field behavior, no subordination of motives, instantaneous desires, lack of predictability
Self-awareness and self-esteem	An image of one's self; awareness of their place in the system of public relations; the pursuit of socially meaningful and socially evaluative behaviour.	After four years of the first manifestations of self-consciousness, this is reflected in the negative reactions to comments, condemnation, failure.

are inhibited: memory, perception, thinking, poorly developed speech, there is a significant underdevelopment of motor skills. Thus, psychological and pedagogical analysis of the literature shows that the underdeveloped thinking of older preschool children affects all areas of the child's development: productive activity, personality, speech and communication. Self-mastering skills are slow and unsatisfactory. Lately, a phrase language that is characterized by a sufficiently depleted vocabulary, lack of detailed answers, cannot make up the picture. The stock of household information is scarce. Does not understand or

understand the concept of color and number. Game activity is very primitive and has signs of imitation.

The child cannot establish contacts with other children because he does not understand the rules of play, interests, motives of other children. Feelings develop and differentiate. Development of pity, compassion, understanding of pain and suffering of another person is delayed.

**Conclusions.** Theoretical analysis of the features of thinking and mental processes of the senior preschooler made it possible to state that children with intellectual disabilities are characterized by weakness and imbalance of

nervous processes; disorders of plasticity and mobility of the nervous system; involuntary, unstable and low attention span; disturbance of sensations of different modality, as a result of distorted perception of objects and situations; all mental processes that are characteristic of a preschooler with normal development (creativity, initiative, independence and responsibility, arbitrariness, freedom of behavior and safety, self-awareness and self-esteem) occur very slowly, without active motivation for any kind of activity, for the environment, for social phenomena; researchers emphasize the passive attitude of such preschoolers to their peers to adults, to themselves; visual and spatial perception disorders; small amount of memory (difficulty remembering and playing material); inhibited initiative, passive perception of reality, low cognitive motivation; main activity is not game, but subject; the game is stereotyped, formalized; broadcasting is detached from activity; passive vocabulary far exceeds active; have difficulty in regulating behavior, overcoming obstacles, completing a case, there is no need to manage their behavior.

Thinking of a senior preschooler with intellectual disabilities is characterized by the following features: disorders of all mental operations (to a greater extent abstraction, generalization); decrease in activity of thought processes, not activity in search of the solution, indifference to the result and process of solving even the game problem; speech development; thinking is formed in conditions of defective sensory cognition; limited practical activity; the most preserved kind of thinking - visual and effective; unawareness and chaotic actions in the process of solving problems; not critical thinking; weak regulatory role of thinking; low motivation of mental activity; significant lag in the pace of development; poorly oriented in space, unable to evaluate the properties of objects and the relationship between them; concreteness and situationality of thinking, weakness of generalizations; there is no possibility of solving visual problems.

We see the prospects for further research in the theoretical substantiation, development, implementation and evaluation of the effectiveness of the program-methodological complex of thinking development for children of preschool age by means of non-traditional

pictorial activity. As a result of theoretical analysis of the mental and mental development of preschool children with intellectual disabilities, it is found that without special corrective training, this development will be insufficient and will significantly deviate from the development of normal preschoolers.

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## LONG-TERM RESULTS OF COMPLEX TREATMENT WITH CHRONIC GENERALIZED PERIODONTITIS AND A PREDOMINANCE OF THE SYMPATHETIC AUTONOMIC NERVOUS SYSTEM

**Abstract.** *The features of the clinical course of many diseases depend on the state of the patient's autonomic system, in particular, the predominance of the sympathetic or parasympathetic autonomic nervous system. Given the close relationship of the vascular and nervous systems of the periodontium, the vegetative nervous system has an integrating role. This should be taken into account when treating patients with chronic periodontitis, since these patients have certain problems with the state of general resistance. Given this, the proposed drug treatment regimen for the treatment of generalized periodontitis in patients with a predominance of the sympathetic autonomic nervous system. Aim. The determination of the long-term results clinical efficacy of the proposed complex treatment of patients with chronic course of generalized periodontitis in the presence of sympathetic nervous system predominance. Materials and methods. Clinical investigation was conducted on groups of 60 patients with chronic course of generalized periodontitis and prevalence of the sympathetic nervous system.. Medicamental treatment was performed using proposed sedation composition. Patients were conducted a comprehensive examination of periodontal tissue before treatment and after treatment. To evaluate the clinical efficacy of treatment used Schiller-Pisarev test (1962), the index of PMA by C. Parma (1961), OHI-S hygienic index (1964), the vacuum test by Kulazhenko (1961). Results. As a result of the investigation it was found that the usage of the proposed sedation composition in the complex therapy of patients with chronic course of generalized periodontitis can effectively inhibit the dystrophic-inflammatory process in periodontal tissues. This confirms by the decline in the index PMA, increase the time of formation of hematoma during the vacuum tests on Kulazhenko, improving oral hygiene in remote observation terms. Conclusions. Usage of the proposed sedation composition increases the effectiveness of treatment of chronic course of generalized periodontitis in patients with predominance of the sympathetic nervous system.*

**Key words:** *chronic course of generalized periodontitis, patients with predominance of the sympathetic nervous system, sedation composition.*

**Introduction.** A special place in the emergence and development of dystrophic-inflammatory periodontal diseases, belong to their combination with various common somatic diseases [5, 9, 15]. In the integrated treatment of patients with generalized periodontitis, it is necessary to take into account the clinical picture of periodontal disease and the overall health of patient. The presence of certain common somatic diseases has a significant impact on the clinical picture of generalized periodontitis.

The features of the progression of many diseases depend on the condition of the patient's autonomic system, particularly the predominance of the sympathetic or parasympathetic autonomic nervous system (1). The autonomic nervous system plays an integrating role, according to the close

relationship between the vascular and nervous systems of periodontal [3, 7, 8, 11].

This should be considered during the treatment of patients with generalized periodontitis, while these patients have certain problems with the state of general resistance. Thus, in the occurrence and development of degenerative inflammatory periodontal diseases, their combination with various somatic diseases occupies a special place [5, 9, 15].

Without these characteristics, periodontal diseases have an unfavorable effect and resistance to treatment.

For the medical preparation of patients with chronic generalized periodontitis and predominance of the sympathetic autonomic nervous system, before each visit to the dentist it

was prescribed:

1. "Anaprilin" 0.01 g - 1 tablet 2 times a day;
2. Tinctura Valerianae 0.25 drops 3 times a day.

After the dental intervention appoint for 3 days:

1. "Ibuprofen" 0.2 g - 2 tablets 3 times a day;
2. Tinctura Valerianae 0.25 drops 3 times a day;
3. "Anaprilin" 0.01 g of 1 tablet 4 times a day;

To determine the effectiveness of the proposed pharmacological therapeutic and prophylactic drug composition (Utility model patent No. 114198, A method for treating patients with chronic generalized periodontitis, in which the activity of the sympathetic autonomic

nervous system predominates, 02.27.2017.) and to solve the tasks, a clinical laboratory examination and treatment of 60 patients with generalized periodontitis, with a predominance of the sympathetic autonomic nervous system were performed.

Their examination and treatment was carried out during 2016-2018 at the Department of Therapeutic Dentistry of the Higher state educational establishment "Bukovinian State Medical University".

This study presents the long-term results of treatment of patients with chronic onset of generalized periodontitis in case of predominance of the sympathetic nervous system.

The aim of our study was to determine the long-term results of the clinical effectiveness of the proposed complex treatment of patients with generalized chronic periodontitis with the predominance of the sympathetic nervous system.

**Material and methods.** Comprehensive treatment of generalized periodontitis was carried out in a group of 60 patients aged 25-45, with a chronic generalized periodontitis of the I-II degree and the predominance of the sympathetic nervous system in them. Among them were 38 (63.33%) women and 22 (36.67%) men. They were divided into two groups - the main (40 patients) and the group comparison (20 patients). The distribution of patients into groups in accordance with the degree of disease, age and gender was almost the same. 40 patients were amounted to the main group of the study. For their treatment, a drug therapy regimen was developed (Utility model patent No. 114198, A

method for treating patients with chronic generalized periodontitis, in which the activity of the sympathetic autonomic nervous system predominates, 02.27.2017.) Assessment of the autonomic nervous system status was carried out by determining the Kerdo index [14].

A control group consisted of 20 patients with a chronic generalized periodontitis of the first degree with a predominance of the sympathetic nervous system.

The treatment of periodontal disease in them was carried out by generally accepted methods according to the treatment protocols approved by the Ministry of Health of Ukraine, 2004.

Essentially local treatment of both groups of patients with generalized periodontitis was carried out the same. For antiseptic rinses, a 0.5% chlorhexidine bigluconate solution was used. To conduct professional oral hygiene, all patients used a manual toothbrush, flosses, toothpaste and mouthwash "Lacalut". Completely eliminated all periodontal tissue irritants (plaque, calculus, etc.). Subsequently, the complete removal of subgingival dental deposits with the treatment of the tooth roots surface (the so-called SRP - scaling and root planning) was carried out. A comprehensive examination of periodontal tissues was performed for all patients before and after treatment. The severity of the inflammatory process in the gums was assessed using a Schiller-Pisarev test (1962) and the PMA index C. Parma (1961). Hygiene of the oral cavity of patients was determined using the hygiene index OHI-S (1964). The state of vascular permeability of the gums was evaluated using a vacuum test according to Kulazhenko (1961) [4, 10, 12, 13, 16].

For the diagnosis of periodontal disease it was used the classification of periodontal disease according to M.F. Danilevsky [2]. The results were processed by statistical methods using student's personal computers [6]

**Results.** Long-term results of treatment were monitored on the basis of clinical, radiographic and laboratory research methods in terms of 6, 12 and 18 months. After 6 months, 39 (97.5%) patients of the main group were examined, after 12 months 37 (92.50%) and after 18 months, 34 (85.0%) patients.

Similarly, to compare the results, a survey of the corresponding percentage of patients in the group comparison was conducted: after 6 months - 19 (95.0%) , after 12 months - 17 (85.0%) patients and after 18 months - 16 (80.0%) patients. All patients underwent a complex examination of periodontal tissues, as before treatment.

After treatment using the proposed drug premedication, it was observed a satisfactory condition of periodontal tissues in patients of the main group after 6 months in 35 (89.47%) of 39 examined patients, after 12 months - in 32 (86.49%) of 37 patients and after 18 months - in 29 (85.29%) of 34 patients. Accordingly, in the group comparison , satisfactory treatment results were found after 6 months in 15 (78.95%) of 19 patients, after 12 months in 13 (76.47%) of 17 patients and after 18 months in 12 (75.0%) ) from 16 patients examined.

After 6 months, patients of the main group noted the absence of unpleasant subjective sensations in the oral cavity, soreness , bleeding , feeling of heaviness and itching in the gums. The mucous membrane of the gums was dense, the gingival papillae were not hyperemic. The Schiller-Pisarev test in 33 (84.62%) of the 39 examined was slightly yellow. In patients with I degree of generalized periodontitis, discharge from periodontal pockets was not observed.

The oral cavity hygiene was satisfactory: the hygiene index before treatment was  $1.74 \pm 0.09$  ; after treatment  $0.85 \pm 0.07$ . The level of gum inflammation also decreased, as evidenced by the PMA index -  $9.7 \pm 0.78\%$  after treatment and after 6 months it only slightly increased - up to  $10.6 \pm 0.95\%$ .

In patients with II degree of generalized periodontitis, slight deposits of calculus were noted. The depth of periodontal pockets was at the level obtained after treatment. The discharge from them was noted in 6 (15.38%) patients, they were in a small amount of serous nature. The X-ray signs of stabilization of the pathological process in the periodontium were noted.

The positive clinical results of treatment were confirmed by laboratory data. Vacuum hematoma formed on average after  $37.2 \pm 3.8$  , which is even

higher than immediately after treatment. Indicators of leukocyte migration into the oral cavity were approximately at the same level. In periodontal pockets, a small amount of microflora was noted. Mostly cocci and mixed flora prevailed (in a small amount the same as after treatment, yeast-like fungi and protozoa were found). In the cellular composition of pockets, neutrophilic granulocytes, polyblasts and epithelial tissues prevailed.

In patients of group comparison, similar satisfactory clinical, radiological and laboratory results of treatment were noted in 16 (84.21%) of 19 patients. In 2 (10.53%) of them, a further slight progression of the dystrophic-inflammatory process was noted. Clinical laboratory indicators in the group comparison were satisfactory, but slightly lower than in the main group of patients with generalized periodontitis. Thus, the occurrence of certain complications in the group comparison can be considered as a consequence of the aggravation of the dystrophic-inflammatory process in periodontal disease.

12 months after the treatment, 37 (92.50%) patients of the main group and 17 (85.0%) patients of the group comparison were examined. In 30 (81.08%) of 37 patients of the main group, there was a lack of unpleasant subjective sensations in the oral cavity, soreness, bleeding and itching in the gums. The mucous membrane of the gums was dense. The gingival papillae were not hyperemic. The Schiller-Pisarev test was slightly yellow in 12 (32.43%) of the 37 examined. The state of oral cavity hygiene was satisfactory: the OOI-S hygiene index before treatment was  $1.74 \pm 0.09$  and decreased to  $0.84 \pm 0.06$  points after treatment. The gum inflammation also decreased, as evidenced by the PMA index -  $9.7 \pm 0.78\%$ , and after 12 months -  $11.45 \pm 1.15\%$ .

Dental deposits were noted in a small amount in 5 (13.51%) of 37 patients. Pathological tooth mobility was significantly lower than before treatment.

The depth of periodontal pockets remained at the level reached immediately after treatment. Radiologically, the phenomena of osteoporosis in the alveolar bone of the jaw were lower than

before treatment. The height of the interalveolar septa remained at the same level.

The obtained clinical laboratory examinations demonstrated the stabilization of the dystrophic-inflammatory process in the periodontium of this category of patients.

In patients with positive clinical results, it was maintained gum capillaries stability, achieved after treatment. Vacuum hematoma formed on average after  $35.4 \pm 1.2$  s, which can be considered as a satisfactory result. The amount of neutrophils that migrated to the oral cavity remained almost at the same level achieved after treatment. The total number of cells in the content of periodontal pockets was lower; neutrophilic granulocytes, polyblasts and epithelial cells prevailed.

The amount of microflora was lower than before the treatment, but more than in the group comparison. Cocci prevailed, mixed microflora and yeast-like fungi remained at the same level. In patients of group comparison, similar satisfactory clinical, radiological and laboratory treatment results were noted in 12 (70.59%) of 17 patients. In 3 (17.65%) of them, further slight progression of the dystrophic-inflammatory process was noted (in these cases, exacerbation of the pathological process was treated). Clinical quality indicators in the group comparison were satisfactory, but slightly lower than in the main group of patients with generalized periodontitis. The results obtained indicate to the positive comparative clinical laboratory results of the patients treatment with generalized periodontitis using the proposed drug premedication.

18 months after treatment, 30 (88.24%) of 34 patients of the main group and 14 (87.5%) of 16 patients of the group comparison were examined. In 25 (83.33%) of 30 patients of the main group and in 10 (71.43%) of 14 examined patients of the group comparison a satisfactory condition of periodontal tissues was found. The gingival mucosa was dense, hyperemia of the gingival papillae was absent in 25 (83.33%) of the 30 patients of main group and in 10 (71.43%) of the 14 patients of the group comparison.

The Schiller-Pisarev test was negative in 23 (76.67%) of 30 patients of the main group and 10

(71.43%) of 14 patients of the group comparison. In another part of the patients, it was yellow. The state of oral cavity hygiene was satisfactory: the hygiene index before treatment was  $1.74 \pm 0.09$  and  $0.89 \pm 0.06$  after treatment. The level of gum inflammation also decreased, as evidenced by the PMA index -  $9.7 \pm 0.78\%$  after treatment and after 18 months -  $11.55 \pm 1.15\%$  (Table 1). An insignificant amount of dental plaque was noted in 7 (42.42%) of 30 patients of the main group and in 6 (52.94%) of 16 patients of the group comparison. Pathological tooth mobility and the depth of periodontal pockets remained at the level achieved after treatment in 25 (83.33%) of 30 patients of the main group and 10 (71.43%) of 14 patients of the group comparison. Radiologically, the phenomena of osteoporosis in the alveolar bone of the jaw were lower than before treatment. The height of the interalveolar septa remained at the same level. The stability of the gum capillaries, which was achieved immediately after treatment at the level of vacuum hematoma formation after an average of  $34.5 \pm 2.5$  s, was maintained, which can be considered as a satisfactory result. The number of neutrophils migrating into the oral cavity in the majority - 26 (86.67%) of the 30 patients of the main group and in 12 (75.00%) of the 16 patients of the group comparison remained almost at the level reached after treatment (Table 5.27).

The total amount of cells in the periodontal pockets was at the level obtained immediately after treatment, neutrophilic granulocytes, polyblasts and epithelial cells prevailed. The number of microflora was slightly increased, but was lower than in the similar group comparison. Cocci prevailed, mixed microflora and yeast-like fungi were at the same level. The obtained data from clinical laboratory examinations indicate to the stabilization of the dystrophic-inflammatory process in the periodontium of this category of patients (Table 1-3); also, it was observed the pronounced beneficial effect of the proposed drug premedication usage in the treatment of patients with generalized periodontitis with a predominance of the sympathetic autonomic nervous system.

Table 1

**The dynamics of clinical quality indicators in patients with generalized periodontitis with the predominance of the sympathetic autonomic nervous system 18 months after treatment**

Clinical quality indicators	Main group				Group control			
	Before treatment	After treatment	18 months after treatment	p <sub>1</sub>	Before treatment	After treatment	18 months after treatment	p <sub>1</sub>
OHI-S (scores)	1,74±0,09	0,67±0,06 p <sub>2</sub> >0,05	0,89±0,06 p <sub>2</sub> <0,05	<0,05	1,79±0,08	0,81±0,06	1,05±0,08	<0,05
Schiller-Pisarev test (scores)	2,8±0,25	1,35±0,11 p <sub>2</sub> <0,05	1,55±0,15 p <sub>2</sub> <0,05	<0,05	2,85±0,25	1,65±0,12	1,9±0,12	<0,05
PBI (scores)	2,66±0,3	0,67±0,04 p <sub>2</sub> <0,05	0,76 ±0,02 p <sub>2</sub> <0,05	<0,05	2,62±0,48	0,81±0,04	1,09±0,04	<0,05
The depths of periodontal pockets (mm)	2,7±0,37	0,82±0,03 p <sub>2</sub> >0,05	1,05±0,02 p <sub>2</sub> >0,05	<0,05	2,7±0,35	1,1±0,02	1,5±0,02	<0,05
PMA (%)	60,25±2,45	9,7±0,78 p <sub>2</sub> <0,05	11,55±1,15 p <sub>2</sub> <0,05	<0,05	60,35±3,51	13,46±0,98	18,33±1,25	<0,05
The periodontal index	2,66±0,3	0,67±0,04 p <sub>2</sub> >0,05	0,85±0,07 p <sub>2</sub> >0,05	<0,05	2,52±0,48	0,89±0,07	1,29±0,08	<0,05
Vacuum test according to Kulazhenko (s)	12,6±1,2	36,3±2,4 p <sub>2</sub> <0,05	34,5±2,5 p <sub>2</sub> <0,05	<0,05	9,8±0,5	20,4±1,1	24,3±1,1	<0,05

Note: p<sub>1</sub> – the indicator of the difference reliability between the main group and the group comparison before and after treatment;

p<sub>2</sub> – the indicators of difference reliability between the main group and group comparison after treatment;

Table 2

**The dynamics of leukocyte migration into the oral cavity in patients with generalized periodontitis with predominance of the sympathetic autonomic nervous system 18 months after treatment (cells in 1 mm<sup>3</sup> of flushing liquid)**

Groups of patients	Time of the survey	Neutrophil Granulocytes	p <sub>1</sub>	Of them alive (%)	p <sub>1</sub>	Cells of desquamated epithelium	p <sub>1</sub>
Main group	Before treatment	376,6±36,3	<0,05	58,6±5,1	<0,05	188,6±8,4	<0,05
	After treatment	182,7±16,8 p <sub>2</sub> <0,05		82,7±6,3 p <sub>2</sub> >0,05		96,5±8,3 p <sub>2</sub> <0,05	
	18 months after treatment	226,5±14,8 p <sub>2</sub> >0,05	<0,05	80,5±3,5 p <sub>2</sub> >0,05	<0,05	88,5±6,4 p <sub>2</sub> <0,05	<0,05
Group comparison	Before treatment	386,4±25,2	<0,05	72,8±4,6	>0,05	206,2±9,7	<0,05
	After treatment	257,7±14,3		84,3±6,6		117±8,4	
	18 months after treatment	298,5±12,4	<0,05	86,3±3,5	>0,05	98,4±9,3	<0,05

Note: p<sub>1</sub> – the indicator of the difference reliability between the main group and the group comparison before and after treatment;

p<sub>2</sub> – the indicators of difference reliability between the main group and group comparison after treatment;

Table 3

**The dynamics of cytologic content of periodontal pockets in patients with generalized periodontitis with predominance of the sympathetic autonomic nervous system 18 months after treatment (% detection)**

Clinical quality indicators	Main group				Group control			
	Before treatment	After treatment	18 months after treatment	p <sub>1</sub>	Before treatment	After treatment	18 months after treatment	p <sub>1</sub>
Epithelial	8,33±0,5	13,32±0,9 p <sub>2</sub> <0,05	14,88±0,9 p <sub>2</sub> <0,05	<0,05	5,56±0,5	8,32±0,8	8,55±0,8	<0,05
Neutrophil Granulocytes: unchanged	31,35±2,13	39,67±1,35 p <sub>2</sub> <0,05	38,55±1,35 p <sub>2</sub> <0,05	<0,05	26,36±2,17	35,17±2,25	31,25±1,25	<0,05
Macrophages	0,39±0,12	1,88±0,37 p <sub>2</sub> <0,05	1,85±0,25 p <sub>2</sub> <0,05	<0,05	0,51±0,12	0,91±0,15	0,95±0,15	<0,05
Destroyed	65,73±3,65	44,74±3,18 p <sub>2</sub> <0,05	46,5±2,15 p <sub>2</sub> <0,05	<0,05	63,12±3,81	53,12±2,53	56,67±2,67	<0,05
Lymphocytes	0,55±0,15	1,56±0,21 p <sub>2</sub> >0,05	1,64±0,21 p <sub>2</sub> >0,05	<0,05	0,61±0,18	1,23±0,21	1,35±0,21	<0,05
Polyblasts	0,67±0,15	1,51±0,17 p <sub>2</sub> >0,05	1,69±0,16 p <sub>2</sub> >0,05	<0,05	0,59±0,15	1,25±0,15	1,28±0,13	<0,05

Note: p<sub>1</sub> – the indicator of the difference reliability between the main group and the group comparison before and after treatment;

p<sub>2</sub> – the indicators of difference reliability between the main group and group comparison after treatment;

**Conclusions.** Conducted clinical examination in the long term observation of patients with chronic generalized periodontitis of the main group with a predominance of the sympathetic autonomic nervous system after complex treatment, showed a significant decrease in the level of inflammation in periodontal tissues. Thus, the proposed scheme of drug treatment and inclusion in the complex therapy of the proposed drug preparation allows to achieve significant effectiveness of treatment of patients with generalized periodontitis with predominance of the sympathetic nervous system in long-term observation.

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## MORPHOLOGISCHE BESONDERHEITEN BEI JUNGEN ALTAISCHEN KAMPFSPORTLERN

**Anmerkung.** Die Arbeit befasst sich mit Sportlern, die im Kampfsport tätig sind. Sie leben im Altai-Gebirge. Den Athleten wurden die Gesamtkörpergröße, die Längsabmessungen, die Umfangsabmessungen, die Dicke der Fettschichten und die Skelettmaße gemessen. Basierend auf der Analyse der Daten wurden Schlussfolgerungen gezogen.

**Stichworte:** Morphologie, Anthropologie, Sportler, Gesamtkörpergröße, Altai-Gebirge, Längsabmessungen des Körpers. Dicke der Haut und Fettschichten.

Gorny Altai ist eine Bergregion in der Mitte des Kontinents. Die Einzigartigkeit der Natur dieser Region ist durch Vorhandensein von verschiedenen Klimazonen (Tundra, Schnee- und Gletschergebiete, Alpin-, Subalpin- und Wiesengebiete, sowie Steppen- und Waldsteppengebiete) und durch das Flach- (bis 1500 m), Mittel- (von 1500 bis 3000 m) und Hochgebirge (über 3000 m) geprägt [4].

Das Ziel unserer Forschung ist die morphologischen Besonderheiten bei jungen Kampfsportlern von der Region Gorny Altai unter Berücksichtigung von ethnischen, sozialen und klimatischen Bedingungen ermitteln. An der Studie nahmen 68 männliche altaische Sportler im Alter von 17 bis 25 Jahren teil [2].

Das Untersuchungsprogramm schloss anthropometrische Messungen ein, welche nach der Standardmethodik des Forschungsinstituts und Museums für Anthropologie der Lomonossow-Universität Moskau durchgeführt wurden [1].

Im Rahmen der Untersuchungen wurden die Körpermessungen, einschließlich Längen-, Umfangs- und Skelettmaße sowie die Messungen der Hautfettfaldendicke vorgenommen. Anhand der erhaltenen Werte wurde die Fett-, Skelett- und Muskelmasse analytisch berechnet (nach der Formel von Matejko) [3]. Die Körperfläche wurde mithilfe der Formel von Jackson (1958) ermittelt [3].

Alle Kampfsportler wurden in zwei Untersuchungsgruppen je nach ihrer Sportleistungen gemäß der einheitlichen Sportklassifizierung eingeteilt. In die erste Gruppe (40 Personen) wurden Spitzensportler mit dem Titel „Meisterkandidat“ oder höher eingestuft. Das Durchschnittsalter von Sportlern dieser Gruppe lag bei 23,5 Jahren. Der zweiten Gruppe (28 Personen) wurden angehende Sportler ohne Titel

bzw. mit niedriger Leistungsklasse mit dem Durchschnittsalter von 23,5 Jahren zugeordnet.

Im Rahmen der Vergleichsanalyse von zwei Probandengruppen wurden in erster Linie Körpermessungen vorgenommen, denn sie sind für die körperliche Gesamtentwicklung der Sportler ausschlaggebend (Abb. 1). Es ist anzunehmen, dass kontinuierliche Trainingsbelastung und Sporttraining dazu führen, dass hochqualifizierte Sportler von Gorny Altai einen größeren Brustkorb bei kleinerem Gewicht und kleinerer Körperlänge haben.

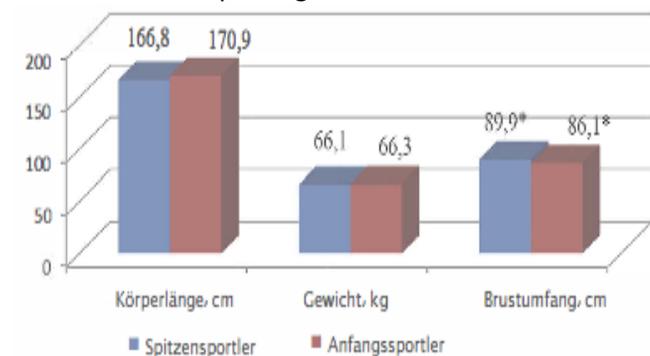


Abbildung 1. Körpermessungen der Sportler von der Region Gorny Altai (\* $p < 0,05$ )

Die von uns vorgenommenen Umfangsmessungen zeugen deutlich davon, dass Werte von hoch qualifizierten Sportlern über denen der angehenden Sportler liegen, was zweifellos aus langjähriger und mehrstufiger Selektion der Sportler resultiert (Abb. 2).

Gemessene Werte der Skelettbreite - die Schultern- und Beckenbreite sowie der Sagittaldurchmesser des Brustkorbes - bei den hoch qualifizierten Sambo-Kämpfern aus der Region Gorny Altai kennzeichnen sich durch schmale Schultern und Becken sowie den vergrößerten Durchmesser des Brustkorbs (Abb. 3).

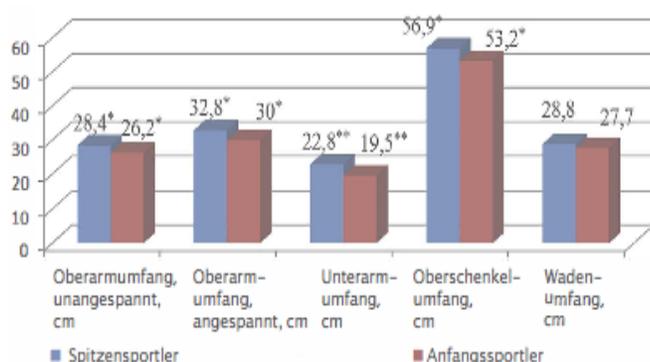


Abbildung 2. Umfangsmessungen der Sportler von der Region Gorny Altai (\* $p < 0,001$ , \*\* $p < 0,0001$ )

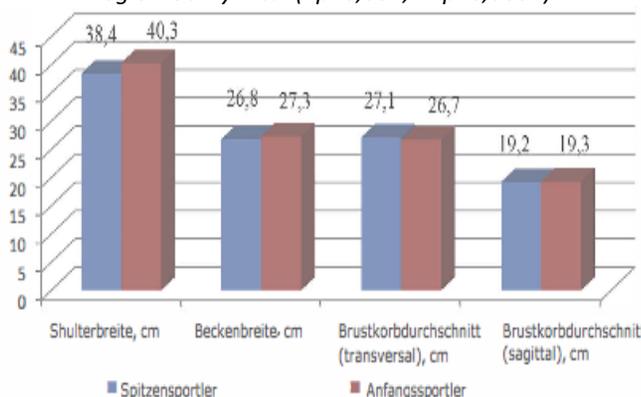


Abbildung 3. Körperbreite der Sportler von der Region Gorny Altai

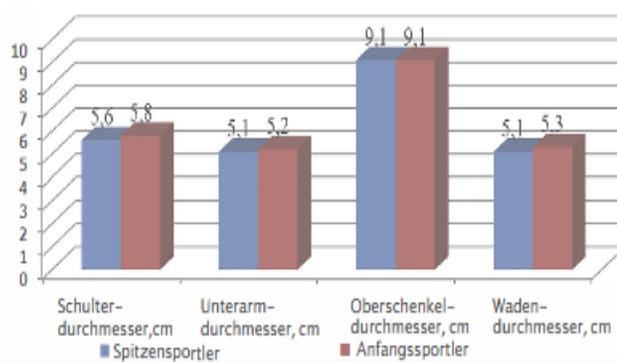


Abbildung 4. Die Durchmesser der distalen Epiphysen bei Sportlern von der Region Gorny Altai

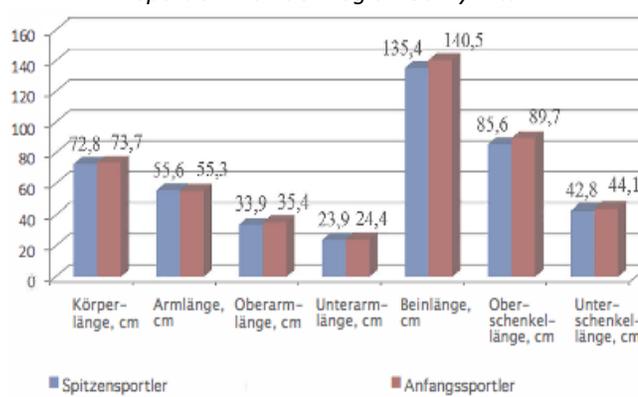


Abbildung 5. Längenmessungen der Sportler von der Region Gorny Altai (\* $p < 0,05$ )

Durchmesser von distalen Epiphysen bei den Spitzensportlern weisen fast gleich hohe Werte wie die bei den angehenden Sportlern auf, abgesehen vom Durchmesser des Oberschenkels, bei dem keine Unterschiede festgestellt wurden (Bild 4).

Die Auswertung der Längenmessungen lässt folgende Tendenz feststellen - da die Längenmessungen mit der Körperlänge korrelieren, sind gemessene Skelettlängen bei den Anfangssportlern etwas größer, ausgenommen Armlänge, deren Wert bei den hoch qualifizierten Sportlern etwas höher ist (Abb. 5).

Die zwei Untersuchungsgruppen wiesen verschiedene Dicke der Hautfettfalten auf, obschon die Umfangsmessungen bei den Sportlern beider Gruppen eine gesamte Tendenz zeigten. Durch hohe Bewegungsaktivität und regelmäßige Trainings sinkt die Dicke der Hautfettfalten am Körper der hoch qualifizierten Sportler und baut sich die Muskelmasse auf, wovon die dünne Fettschicht an Gliedern bei gleichzeitig großen Umfangswerten zeugt.

Vergleicht man die gemessene Dicke der Hautfettfalten, stellt man folgende Besonderheiten fest: die Spitzensportler weisen am Rücken, an der Hinterschulter, am Unterarm, an der Brust und am Unterschenkel deutlich kleinere Falten als angehende Sportler auf. Dies ist durch eine hohe Bewegungsaktivität und regelmäßige Sporttrainings zu erklären. Dieser Faktor reduziert die Fettfaltenbildung

am Körper und fördert die Entwicklung der Muskelmasse. Die Spitzensportler haben an der Brust und am Bauch eine dickere Fettschicht, was jedoch keine signifikante Differenz darstellt (Abb. 6).

Wie bekannt ist, weisen die Muskelmasse- und Fettwerte den allgemeinen und speziellen Trainingszustand auf. Im Rahmen unserer Studie wurde der aktuelle morphologische Zustand (Fett-, Muskel- und Knochenanteil) bewertet. Untersuchungsergebnisse zeigen, dass absolute Werte der Muskel- und Fettmasse bei den Spitzensportlern deutlich höher als bei den angehenden Sportlern sind. Hinsichtlich der Knochenmasse liegen die Anfangssportler jedoch über den hoch qualifizierten Sportlern, was aber nicht wundert, denn die bei den angehenden Sportlern gemessenen Werte der Knochenenddiaphyse waren ursprünglich größer (Abb. 7). Analysiert man die morphologischen Werte der Gruppe von angehenden Sportlern, sieht man einen größeren Knochenanteil, was sich in der gesamten Körpergröße widerspiegelt. Die Anfangssportler sind hochwüchsiger, haben längere Glieder und einen breiteren Körper als die Spitzensportler. Dabei weisen Ergebnisse der Umfangsmessungen bei den angehenden Sportlern niedrigere Werte als bei den hochqualifizierten Sportlern von der Region Gorny Altai auf. Die Anfangssportler stehen ebenso in puncto Brustumfang nach.

Die hoch qualifizierte Sportler haben größere

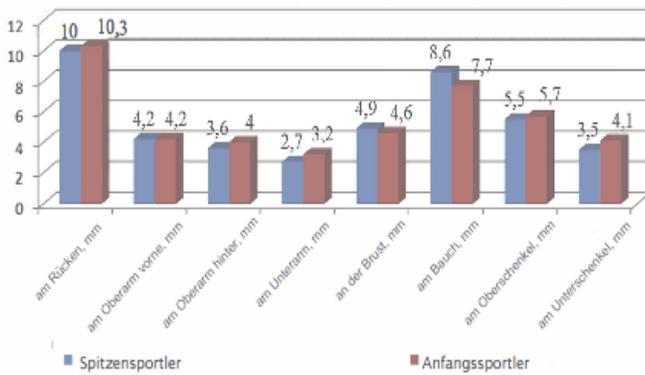


Abbildung 6. Hautfettfalten bei den Sportlern von der Region Gorny Altai

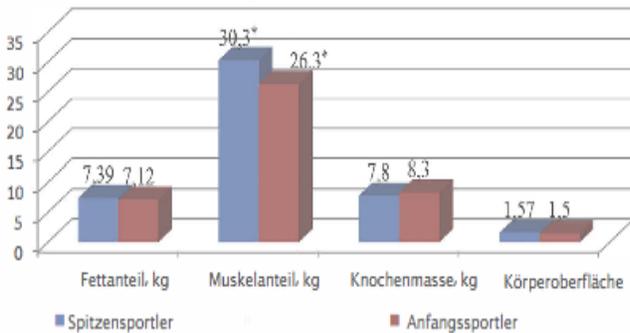


Abbildung 7. Körperanteile bei den Sportlern von der Region Gorny Altai (\* $p < 0,001$ )

Umfangswerte, einen längeren Rumpf, längere Arme und dickere Hautfettfalten an der Brust und am Bauch im Vergleich mit den angehenden Sambo-Kämpfern von der Region Gorny Altai. Die Körperanteil-Analyse weist einen höheren Fett- bzw. Muskelanteil sowie eine größere Körperoberfläche bei den hoch qualifizierten Sportlern als bei den Sportlern ohne Qualifikation auf.

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## INVESTIGATION OF THE IMPACT OF AMANTADINE SULPHATE ON CERTAIN PATHOGENETIC MECHANISMS OF TRAUMATIC BRAIN INJURY

**Abstract.** *The goal of the work to characterize the effect of amantadine sulfate compared with 0.9% NaCl solution on the course of oxidative stress in the brain of rats with traumatic brain injury. The experiments were performed on white male rats weighing 160-190 g. Treatment of rats with TBI with amantadine sulfate leads to a decrease in the activity of lipid peroxidation processes and oxidative destruction of proteins ( $p < 0,05$ ) and helps to normalize the activity of antioxidant enzymes in cells of traumatically damaged brain ( $p < 0,05$ ). The use of amantadine sulfate compared with 0,9% NaCl solution was accompanied by a more significant decrease in the activity of lipid peroxidation processes and oxidative destruction of proteins and an improvement in the level of antioxidant enzymes in damaged brain of animals with TBI ( $p < 0,05$ ).*

**Keywords:** *traumatic brain injury, amantadine sulfate, rats.*

**Introduction.** The analysis of the literature indicates that, in the case of brain damage, hyperproduction of reactive oxygen species by brain tissues is registered, which activates the development of oxidative and nitrosative stress of proteins, lipids and nucleic acids of neurons in its structures, violates the affinity and specificity of receptors, generation of action potentials and conduction of nerve impulse [1, 2]. Therefore, the use of pharmacotherapeutic agents with antioxidant properties is an important measure of intensive care in patients with traumatic brain injury (TBI) [3]. Many studies on the treatment of nosology accompanied by both traumatic and ischemic brain damage have demonstrated the efficacy of glutamate NMDA receptor antagonists. Blockade of NMDA receptors is considered to be one of the main links in neuroprotection [4, 5, 6]. That is why it was expedient to investigate the effect of amantadine sulfate in a difficult TBI experimental model on the course of TBI oxidative stress as a drug capable of blocking NMDA receptors.

**Materials and methods.** The experiments were performed on white male rats weighing 160-190

g, which were in standard vivarium conditions, in accordance with the ethical standards of experimental studies. Rats under conditions of propofol anesthesia were performed right-sided bone-plastic trepanation of the skull in the projection of the middle cerebral artery and simulated severe TBI. The therapeutic effect of amantadine sulfate ("PC-Mertz", Merz Pharmaceuticals, Switzerland) at a concentration of 200 mg / 500 ml on model TBI was evaluated by the administration of a dose of 5 mg / kg intravenously. Treatment was performed by slow intravenous (i/v) infusion with infusomate every 12 h for 8 days. Treatment was started 1 h after simulation of the pathological condition. Pseudoperated animals were subjected to all interventions (anesthesia, skin incision, skeletal bone-plastic trepanation) with the exception of manipulations that could directly lead to traumatic brain injury, which eliminated the effects of traumatic conditions of the experiment. They were also administered an equivalent amount of 0.9% NaCl solution up to a dose of amantadine sulfate. As a drug for the control group we used 0.9% NaCl solution at a dose of 2

ml / kg i/v the same mode.

Biochemical processes in traumatically damaged brain were investigated on the 8th day of TBI. The content of malondialdehyde (MDA) - by reaction with thiobarbituric acid, carbonyl groups of proteins (CGP) - by reaction with 2,4-dinitrophenylhydrazine. The activity of superoxide dismutase (SOD) was evaluated by the percentage of inhibition of quercetin oxidation, and catalase by the rate of degradation of hydrogen peroxide. The activity of glutathione peroxidase (GPO) was determined by spectrophotometric method with the accumulation of oxidized glutathione [7]. Quantitative data were processed using the StatPlus 2009 statistical processing program.

**Results and Discussion.** Nowadays, many current experimental and clinical studies are aimed at finding effective molecules that can prevent secondary neuronal damage caused by the multifaceted pathogenetic mechanism of brain damage in TBI. The action of NMDA receptor blockers is aimed at inhibiting the rapid responses of the glutamate calcium cascade, which can reduce secondary damage to neurons against TBI [5, 6]. Under the conditions of experimental TBI, it was found that hyperactivation of free radical oxidation of biomembrane lipids is registered in the structures of the brain of rats (fig. 1). In the group of pseudoperated animals, the median content of

the secondary metabolite of malone dialdehyde (MDA) in the brain is 13,2 (95% CI 12,8-14,2)  $\mu\text{mol} / \text{g}$  of dry tissue, and the percent interval  $P_{25}\text{-}P_{75}$  - 13,1-14,0  $\mu\text{mol} / \text{g}$  of dry tissue. At the same time, in animals of the control pathology group, this indicator is 2,28 times ( $p < 0,05$ ) higher than in pseudoperated animals, its median is equal to 30,8 (95% CI 28,6-33,3)  $\mu\text{mol} / \text{g}$  of dry tissue, and the percentile interval  $P_{25}\text{-}P_{75}$  is in the range of 29,4-31,8  $\mu\text{mol} / \text{g}$  of dry tissue. In the ability to inhibit lipid peroxidation, amantadine sulfate was superior to the TBI + NaCl group. In animals treated with amantadine sulfate, the MDA content in the brain was lower by 48,4% ( $p < 0,05$ ) than in the animals of the control pathology group, the median was 16,1 (95% CI 14,9-16,7)  $\mu\text{mol} / \text{g}$  of dry tissue, and the percentile interval  $P_{25}\text{-}P_{75}$  of 15,5-16,3  $\mu\text{mol} / \text{g}$  of dry tissue.

The development of TBI is associated with the activation of oxidative modification of proteins (fig. 2). In pseudoperated animals, the median content of carbonyl groups of proteins (CGP) in the brain is 4,73 (95% CI 4,29-5,01)  $\mu\text{mol} / \text{g}$  of dry tissue, and the percentile interval  $P_{25}\text{-}P_{75}$  is 4,57-4,94  $\mu\text{mol} / \text{g}$  of dry tissue. On the other hand, at TBI the level of carbonylated proteins was 1,77 times ( $p < 0,05$ ) higher than in pseudoperated animals, its median was 8,66 (95% CI 7,89-9,67)  $\mu\text{mol} / \text{g}$  of dry tissue, and the percentile interval  $P_{25}\text{-}P_{75}$  was in the range of 8,17-9,28  $\mu\text{mol} / \text{g}$  of dry tissue. The use of amantadine sulfate inhibits

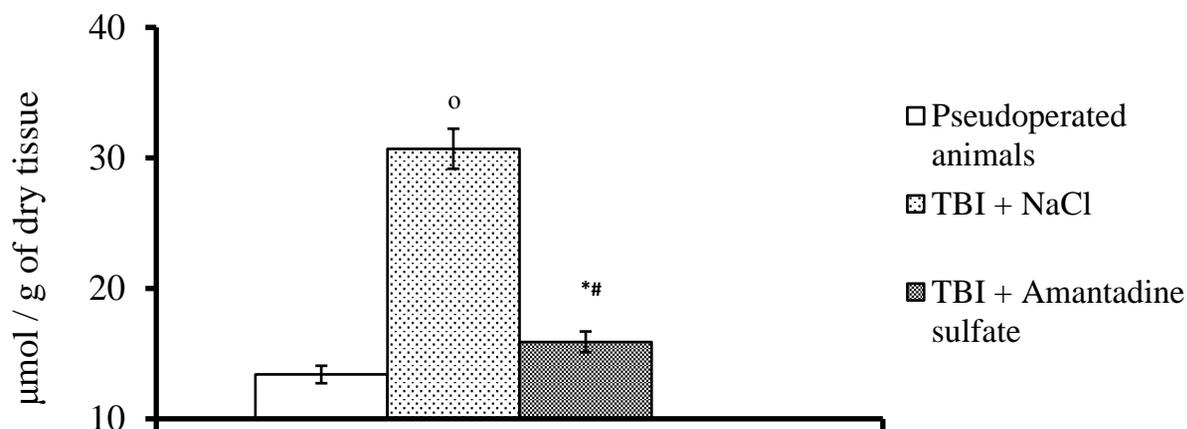


Fig. 1. Effect of a course 8-day infusion of amantadine sulfate on the content of lipid peroxidation products in the brain of rats with TBI ( $M \pm m$ ,  $n=7$ ).

Notes:

TBI - traumatic brain injury;

o -  $p < 0,05$  relative to pseudoperated animals;

\* -  $p < 0,05$  relative to the control pathology group

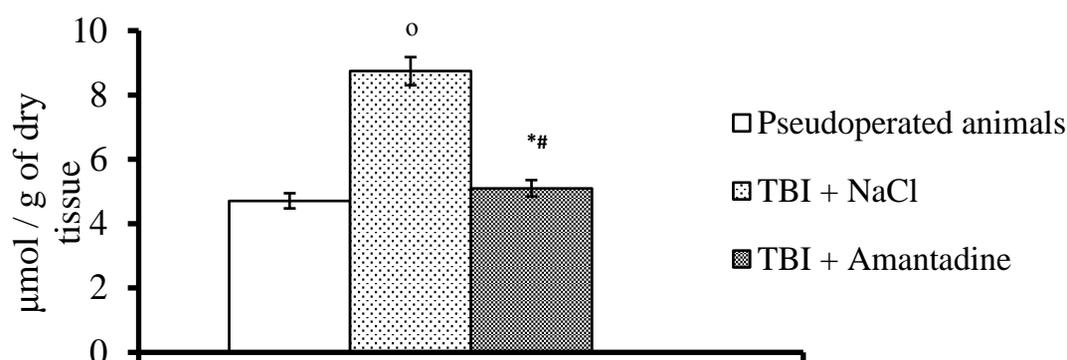


Fig. 2. Effect of a course 8-day infusion of amantadine sulfate on the content of protein peroxidation products in the brain of rats with TBI ( $M \pm m$ ,  $n=7$ ).

Notes:

TBI - traumatic brain injury;

o -  $p < 0,05$  relative to pseudoperated animals;

\* -  $p < 0,05$  relative to the control pathology group.

the activation of the processes of oxidative degradation of proteins in brain tissues. Thus, in animals treated with amantadine sulfate, the CGP content in the brain was 39,1% lower ( $p < 0,05$ ) than in the animals of the control pathology group, the median was 4,99 (95% CI 4,65-5,59)  $\mu\text{mol} / \text{g}$  of dry tissue, and the percentile interval  $P_{25}-P_{75}$  - 4,83-5,39  $\mu\text{mol} / \text{g}$  of dry tissue.

Thus, the use of amantadine sulfate at TBI prevents the hyperactivation of the processes of free radical oxidation of lipids and proteins of brain cell biomembranes.

Hyperactivation of peroxidation of lipids and proteins at TBI occurs against the background of a decrease in the rate of inactivation of the superoxide anion radical. It is established that the median activity of the superoxide dismutation reaction involving SOD in the brain of pseudoperated animals is 2,68 (95% CI 2,23-3,05) c.u / mg of protein, and  $P_{25}-P_{75}$  - 2,50-2,87 c.u / mg of protein. At the same time, at TBI a probable decrease of SOD activity in the brain by 51,7% ( $p < 0,05$ ) is registered, the median activity of this enzyme is 1,31 (95% CI 0,97-1,57) c.u / mg of protein, and  $P_{25}-P_{75}$  - 1,22-1,40 c.u / mg of protein.

Applied pharmacotherapy prevented a decrease in the rate of superoxide anion dismutation reaction in the brain of animals with TBI. In animals treated with amantadine sulfate, SOD activity in the brain was 101% less, its median activity was 2,53 (95% CI 2,09-3,11) c.u / mg of protein, and  $P_{25}-P_{75}$  - 2,28-2,92 c.u / mg of protein.

TBI is accompanied not only by disruption of superoxide anion dismutation in brain cells, but also by inhibition of hydrogen peroxide inactivation with the participation of GPO and catalase enzymes (table 4). In the group of pseudoperated animals, the activity of the GPO varies within 69,3-77,9  $\mu\text{mol} / \text{min}$  per 1 mg of protein, and the activity of catalase in the range of 5,94-7,59  $\mu\text{kat} / \text{mg}$  of protein. However, the development of TBI causes a probable decrease of GPO activity in brain by 70,9% (its activity varies within 32,8-47,2  $\mu\text{mol} / \text{min}$  per 1 mg of protein) and catalase by 46,9% (its activity varies within 3,01-4,16  $\mu\text{kat} / \text{mg}$  of protein).

The pharmacotherapy with the study drug restrained the fall in the activity of the antioxidant enzymes GPO and catalase in brain structures (table). In animals treated with amantadine sulfate, the activity of GPO in brain tissues was higher by 44,5% (ranged from 55,5 to 61,2  $\mu\text{mol} / \text{min}$  per 1 mg of protein) and catalase activity by 79,0% (varied from 6,21 to 6,75  $\mu\text{kat} / \text{mg}$  of protein) than the corresponding indicators in the control pathology group.

According to the results of our studies, we have shown that the use of amantadine sulfate on the background of TBI restrains the fall of the activity of the enzymatic antioxidant link, prevents the accumulation of active oxygen intermediates and slows down the course of reactions of free radical oxidation of lipids and proteins in structures of rats' brain.

Table

**The effect of a course of 8-day infusion of amantadine sulfate on the activity of antioxidant enzymes in the brain of rats with traumatic brain injury ( $M \pm m$ ,  $n=7$ )**

Groups of animals	Enzyme activity	
	GPO, $\mu\text{mol} / \text{min per 1 mg of protein}$	Catalase, $\mu\text{kat} / \text{mg of protein}$
Pseudoperated animals + 0.9% NaCl solution	72,7 $\pm$ 1,37	6,82 $\pm$ 0,26
TBI + 0.9% NaCl solution (control pathology)	40,2 $\pm$ 2,30 <sup>o</sup>	3,62 $\pm$ 0,17 <sup>o</sup>
TBI + amantadine sulfate, 5 mg / kg i/v	58,1 $\pm$ 0,84 <sup>o*</sup>	6,48 $\pm$ 0,08 <sup>o*</sup>

## Notes:

1. TBI - traumatic brain injury;
2. <sup>o</sup> -  $p < 0.05$  relative to pseudoporous animals;
3. \* -  $p < 0.05$  relative to the control pathology group.

**Conclusions:**

1. Treatment of rats with TBI with amantadine sulfate leads to a decrease in the activity of lipid peroxidation processes and oxidative destruction of proteins ( $p < 0,05$ ) and helps to normalize the activity of antioxidant enzymes in cells of traumatically damaged brain ( $p < 0,05$ ).

2. The use of amantadine sulfate compared with 0,9% NaCl solution was accompanied by a more significant decrease in the activity of lipid peroxidation processes and oxidative destruction of proteins and an improvement in the level of antioxidant enzymes in damaged brain of animals with TBI ( $p < 0,05$ ).

**The prospect of further researches.** The therapeutic effect obtained in the experiment from the therapy of amantadine sulfate is the basis for a more in-depth study of the protective effect on the brain at TBI of other NMDA receptor blockers..

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## **PATHOMORPHOSIS OF PERICATRICAL MYOMETRIUM: A NEW VIEW CONCERNING THE PROBLEM OF UTERINE SCAR**

**Abstract.** *Objective of the study was assessment of morphological changes in the myometrium with uterine scar available. Reparative processes in the place of preliminary surgery on the uterine wall among middle-aged women are indicated to occur by means of incomplete regeneration and compensatory hyperplasia of the tissue structural elements. Three years after surgery loose connective tissue has practically transformed into scar tissue, but not completely. To prevent complications with uterine scar available the parity of no less than three years after surgery can be recommended. Pathomorphosis of the pericatricial myometrium differs by imperfect angiogenesis in the scar margins, therefore scar tissues are in the condition of chronic persisting hypoxia, producing in its turn a negative effect on further regeneration.*

**Key words:** *uterine scar, pathomorphosis, pathomorphology, regeneration.*

**Introduction.** An increased number of surgeries on the uterus of women of a reproductive age contributed to cases when on the moment of pregnancy anatomical integrity of the myometrium is changed [1, 3, 9]. A scar available on the uterus increases the risk of complications during pregnancy and labor considerably [1, 3, 7, 9]. It makes special terms for out-patient observation of this group of pregnant women.

Uterine scar can be formed after Cesarean section (in the inferior uterine segment, corporal scar on the uterus), after conservative myomectomy before and after pregnancy (both without opening of the uterine cavity and with its opening). Uterine scar can result from uterine perforation in case of intrauterine surgery – abortions, hysteroscopy, and other traumatic complications. Uterine scars after ectopic pregnancy are known as well (in the interstitial portion of the uterine tube, in the point of junction of the rudiment uterine horn with the main uterine cavity, in the uterine cervix after extraction of the cervical pregnancy). Eventually, uterine scar can form after reconstructive-plastic surgery (Strassman's metroplastic surgery, removal of the uterine rudiment horn etc.). Irrespective of a type of surgery performed the

formation of uterine scar is associated with the risk of its failure changing biomechanics of the endometrium and causing the risk of diastasis and uterine rupture [1, 2, 3, 7, 8].

In recent 20 years sonographic markers of partial or complete failure of the uterine scar have been formulated [1, 3, 11]. Though, till now there is no clear understanding how the myometrium is remodeled in the pericatricial portion. The information concerning morphology of the uterine scar failure suggests the following criteria: 1) foci of connective tissue disorganization in the form of mucoid swelling, fibrinoid swelling and fibrinoid necrosis available; 2) necrosis of leiomyocytes advanced into the scar tissue and located on the border with a scar; 3) intramural hematomas and multiple petechial hemorrhages; 4) inflammatory infiltration of a lymphohistiocytic character with a substantial content of polymorphic-nuclear leukocytes; 5) neoangiogenesis signs [4, 12]. Meanwhile, an accurate notion concerning morphological basis of pathomorphosis of the pericatricial myometrium is still lacking.

After surgical injury reparation processes in the myometrium are considered to occur in the norm at the expense of regeneration of the smooth muscle cells (so-called morphological restitution).

In case of tissue reparation disturbance by the mechanism of substitution reparative processes are found both with disorganization of collagen fibrils and intercellular matrix, pronounced inflammatory reaction, and disturbed angiogenesis [4, 5].

**Objective:** to assess morphological changes in the myometrium with uterine scar available.

**Materials and methods:** the research was conducted on the base of the Regional Perinatal Center and Municipal Establishment «Maternity Home №5» in Odessa during 2017-2019. 426 women with uterine scar were registered during this period including 115 (27,0%) ones with two and more scars. An average age of the examined women was  $33,4 \pm 1,1$ . Three cases of intranatal ruptures of the uterine wall along the “old” scar after Cesarean section were chosen for pathomorphological examination taken from middle-aged women with 33-40 weeks of gestation, without signs of metabolic syndrome, diabetes mellitus, systemic diseases of the connective tissue or other conditions able to disturb reparative processes in the tissues.

The samples of myometrium were preserved in 10 % neutral formalin solution on phosphate buffer (pH 7,2-7,4) during 24 hours. Preparation of histological specimens and their embedding in paraffin were conducted according to the common methods [6]. Microscopy and photography of the specimens were made on the photomicroscope Carl Zeiss (Germany). During histological examination micromorphological structure of the post-surgical scars and the myometrium perifocal tissue was determined. The amount of mitosis per 1000 cells was calculated, and an average distance between the nearest vessels and vascular square were measured.

Immunohistochemical examination was conducted additionally on the series paraffin sections of biopsy material using primary and secondary monoclonal antibodies of Dako sets (USA).

For the quantitative assessment of immunohistochemical examinations the number of cells with immune peroxidase mark (a positive staining) in 10 visual fields randomly selected was calculated under 400-fold microscope magnification (>200 cells) [10]. Proliferative activity index Ki67 (MiB1), collagens of 1 and 3 types, proteins of the muscular tissue intermediate filaments of desmine, and growth

factor of the vascular endothelium and von Willebrand (FW) factor were determined. The above indices were used to assess the level of reparative processes and the state of microscopic surrounding of the scar tissue.

The results obtained were statistically processed by means of nonparametric methods applying the software Statistica 10.0 (Dell StatSoft Inc., USA).

**Results.** Standard staining with hematoxylin and eosin enabled to find the following morphological manifestation: small pieces of the myometrium with pronounced parenchymal dystrophy of myocytes, their wave-like deformity and focal fragmentation (Fig. 1 Photo H&E 3,5,9). The connective tissue is spread among the muscular fibers in the form of eosinophilic linear and star-like mass located mainly around a great amount of thin-walled vessels of a sinusoid type. Single extra-vascular lymphocytes are located perifocally from the foci of sclerosis. Inflammation signs in the surrounding tissue and vascular walls are not found. The following lesions were found in the rupture area against the ground of the above picture: foci of muscular fibers delamination, microfocal necrotic changes of single myocytes, ruptures of the surrounding connective tissue (reparative foci) and fields of hemorrhagic infiltration. Perifocal irregular reactive inflammatory infiltration is found consisting of lymphocytes and macrophages mainly, with single basophils.

The level of proliferative activity index Ki67 in all the samples was less than 2%, which is indicative of the fact that reparative process in the tissue on the moment of intranatal rupture was practically completed.

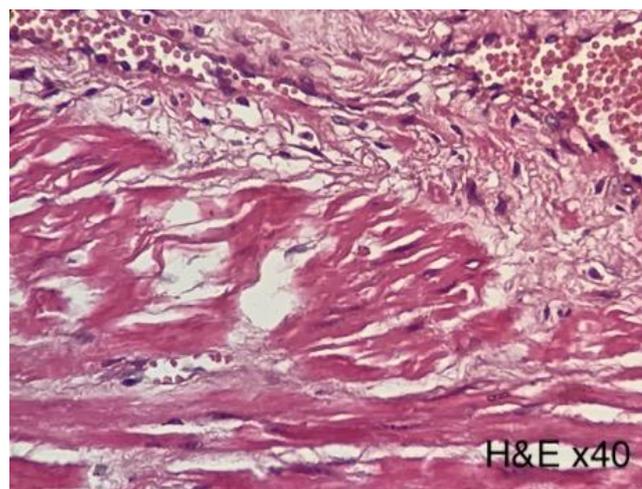


Fig. 1 Morphological picture of uterine scar. Hematoxylin, eosin. Magnification x40

Collagens of I and III types in the scar tissue were characterized by inhomogeneous content. Mostly collagens of I type are located in the form of fibril fractions in spaces between the bundles of the muscular fibers and in the basal membrane of the thin-walled vessels of a sinusoid type in the foci of connective tissue spread (scar tissue). Collagens of III type prevail in the membranes of myocytes, fibrocytes and fibroblasts. They are contained irregularly in the surrounding tissue of the scar margins (Fig. 2a).

Vascular endothelial growth factor (VEGF) is a signal protein produced by a cell under condition of hypoxia. Its function is initiation of neoangiogenesis in the tissue where active reparative process is taking place. It is contained in the intermediate connective tissue, get bounded with an appropriate receptor in the endothelium of a damaged vessel and provokes an active growth of new epithelium. In its turn, it results in the development of thin-walled microvessels as one of the most important human reparation chains. VEGF content in the samples submitted for examination was irregular (Fig. 2b). The immune peroxidase mark is more considerably evident in the tissues of a scar and perifocally in the myometrium, which is indicative of the fact that the tissue is under condition of chronic hypoxia. Irregular staining indicates that hypoxia is persisting.

In its turn, this index can be indirectly assessed as an unfavourable one concerning maturity of the scar tissue. In association with irregular distribution of collagens it is indicative of reduced elastic properties of the scar.

Fon Willebrand (FW) factor is a complex glycoprotein. Its function is provision of platelet attachment to the endothelium of a damaged vessel and thus ensuring hemostasis. FW is expressed by the mature vascular epithelium only. Therefore, it cannot be contained (or be presents in minimum amount) in the microvessels of a sinusoid type. It is this picture shown in the presented samples (Fig. 2c). It should be noted that vascular density on the given samples is rather high. The vessels are mature capillaries mainly, but immature thin-walled vessels are in sufficient amount as well. The distance between the vessels is not long which is indicative of the fact that reparative processes were very active.

Desmine is a protein of intermediate filaments located close to Z-line in the sarcomeres of myocytes. Its examination in the give samples

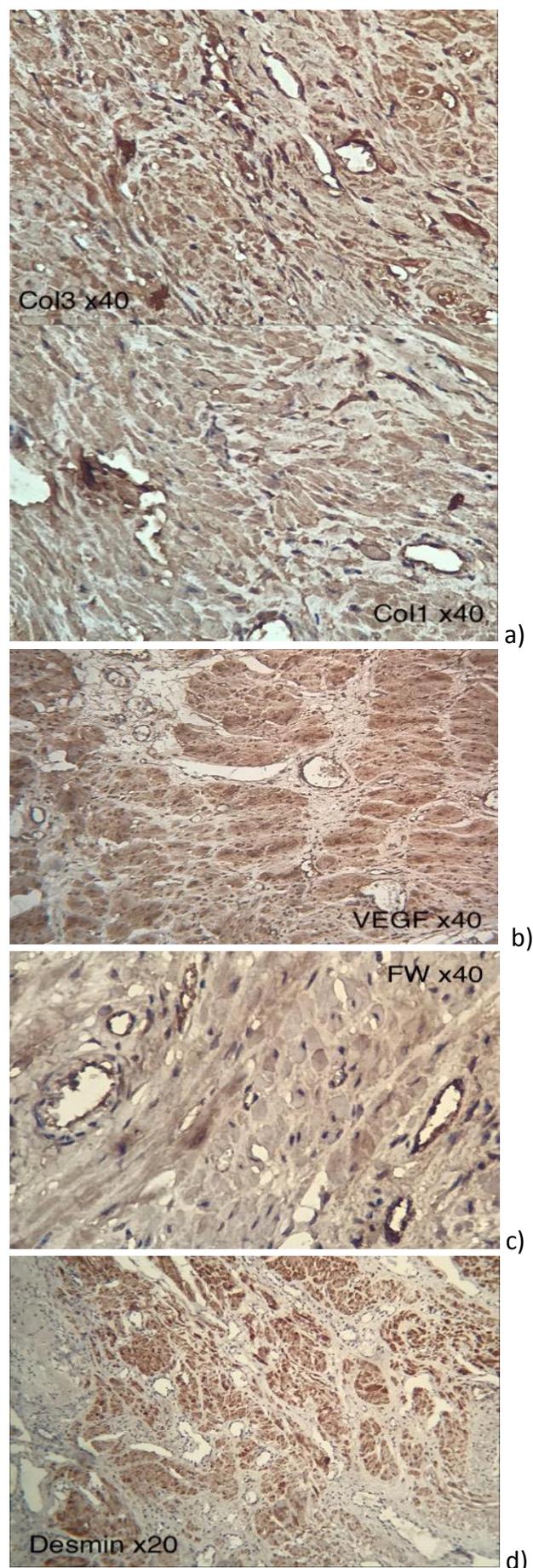


Fig. 2. Expression of the examined proteins by means of immunohistochemical method. Magnification x 400 (a – content of collagens 1 and 3, b – VEGF content, c – FW content, d – desmine content).

was made with the purpose to prove that healing in the postoperative wound occurred by means of incomplete regeneration (substitution), that is, at the expense of the connective tissue spread with compensatory hyperplasia of myocytes and muscular fibers. However, the muscular fibers in the connective tissue of a scar lose their one direction and are located rather chaotically (Fig. 2d). These changes also affect elasticity of the uterine wall in the place of previous surgery.

#### Conclusions:

1. In middle-aged women reparative processes in the place of preliminary surgery on the uterine wall take place by means of incomplete regeneration and compensatory hyperplasia of the tissue structural elements.

2. Three years after surgery loose connective tissue has practically transformed into scar tissue, but not completely. To prevent complications with uterine scar available the parity of no less than three years after surgery can be recommended.

3. Pathomorphosis of the pericatricial myometrium differs by imperfect angiogenesis in the scar margins, therefore scar tissues are in the condition of chronic persisting hypoxia, producing in its turn a negative effect on further regeneration.

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## DIE BESONDERHEITEN DES KLINISCHEN VERLAUFS VON DER ATOPISCHEN DERMATITIS BEI KINDERN BERÜCKSICHTIGEND DIE EIGENSCHAFTEN DER EPIDERMALEN BARRIERE

**Resümee.** Der Forschungszweck: die Besonderheiten des klinischen Verlaufs von der atopischen Dermatitis bei Kindern berücksichtigend die Eigenschaften der epidermalen Barriere untersuchen.

An der Studie nahmen 111 Kinder im Alter von 3 bis 11 Jahren teil, die an atopischer Dermatitis (AD) krank sind. Außer der allgemeinen klinischen Analyse und Bestimmung der spezifischen IgE, um eine kausale Sensibilisierung zu identifizieren, wurde eine molekulare und genetische Analyse durchgeführt (für Etablierung von Polymorphismus im Filaggrine-Gen (FLG)). Die Hautfeuchtigkeit wurde durch die Corneometrie-Methode gemessen. Die statistische Bearbeitung des Materials wurde mit Hilfe der Software Statistica 6 durchgeführt. Es wurde festgestellt, dass es den Polymorphismus im Filaggrine-Protein-Gen bei  $45,9\% \pm 6,98$  Kindern mit AD gibt. Der Polymorphismus R501X wurde bei  $78,4 \pm 5,76\%$  der Kinder nachgewiesen, die Mutation 2282del4 traf bei  $7,8 \pm 3,76\%$  der Patienten, und deren Kombination (R501X und 2282del4) bei  $13,7 \pm 4,81\%$  der Patienten. Der Einfluss der strukturellen Veränderungen des FLG-Proteins auf den morpho-funktionellen Hautzustand wurde festgestellt, der sich durch eine signifikante Abnahme der Feuchtigkeit von Epidermis ( $\chi^2_{20.000001}$ ),  $p < 0,05$  manifestiert. Die Ergebnisse der mikrobiologischen Untersuchung der Haut bei Patienten unter Bedingungen von FLG-Polymorphismus zeigten die Störungen von Mikrobiözönose wie Reduzierung der Mikroorganismen-Kommensalen ( $\chi^2_{21.928}$ )  $p > 0,05$  und Zunahme der Pilzkontamination ( $\chi^2_{6.517}$ )  $p < 0,05$ . Der klinische Verlauf von AD unter FLG-Polymorphismus-Bedingungen ist durch das frühe Debüt (bis zu 3 Monaten),  $P < 0,001$ , und durch den schwereren Verlauf der Krankheit,  $P < 0,001$ ; durch das hohe Sensibilisierungsniveau für Pilz- und Haushaltsallergene,  $P < 0,05$  gekennzeichnet.

**Schlüsselwörter:** atopische Dermatitis, Kinder, Filaggrine, Sensibilisierung.

**Einführung.** Atopische Dermatitis ist eine häufige Hauterkrankung, die oft im Säuglingsalter auftritt [1]. Gemäß der statistischen Angaben wird die Inzidenz von AD in den letzten Jahrzehnten in den Industrieländern stetig gestiegen. Zum Beispiel stieg die Inzidenz von AD bei Kindern in den USA im Jahr 2016 um 17,2 % und in Europa um 15,6% [2]. Inzwischen reicht die Rate der Inzidenz von AD von 6,2 % bis 15,5 % in den Regionen Osteuropas und der Russischen Föderation [3].

Nach den erhaltenen Ergebnisse der internationalen Studie von Asthma und Allergien bei Kindern (International Study of Asthma and Allergies in Childhood), (2012) wurde bei der Untersuchung von etwa 2 Millionen Kindern aus

100 Ländern der Welt festgestellt: hohe Prävalenz von AD bei Kindern in den europäischen Ländern: in Österreich – 9,7-20 %, in Lettland – 5,4-6,5 %, in Polen – 13,2 %. Der AD-Verlauf hat nicht nur territoriale, sondern auch Altersmerkmale: die Prävalenz von AD für Kinder im Alter von 6-7 Jahren reicht von 0,9 % in Indien bis 22,5 % in Ecuador, für Kinder im Alter von 13-14 Jahren – von 0,2 % in China, bis 24 % in Kolumbien, mit höheren Raten in Afrika und Lateinamerika.

Trotz der durchgeführten Studien zur Untersuchung pathophysiologischer Veränderungen im Körper bei AD bleibe eine Reihe von Fragen endgültig unerforscht. Heute wird aktiv die Rolle der genetisch bedingten Erkrankungen in Immunpathophysiologie von AD

diskutiert, insbesondere die Entwicklung von Überempfindlichkeit auf Allergene und unspezifische Reize, wegen der Verletzung des Status von Hautmikrobiom, wie die Kolonisation von pathogenen Mikroorganismen (*Staphylococcus aureus*, *Malassezia furfur*) [3]. Infolge der Vielfalt von Hautmikrobiom und Charakteristik von Biotopen, die überwiegend Vertreter von *Staphylococcus epidermidis*, *Staphylococcus saprofiticus* [4, 5] enthalten, gab es einen bestimmten Einfluss der Mikroflora auf den Zustand der epidermalen Barriere.

Eine wichtige Rolle spielen die Mikroorganismen bei der Bildung des pH-Wertes der Haut. So können einige Bakterien, die ständig auf der Haut leben (vor allem *Staphylococcus epidermidis* und *Lactobacillus*), Säuren produzieren und sich direkt an der Schaffung eines sauren Mantels der Haut beteiligen. Darüber hinaus synthetisiert *Staphylococcus epidermidis* spezifische Verbindungen, die die pathogene Flora unterdrücken können [6]. Die Verletzung der Schutzbarriere führt zu den Abrutschen in der Zusammensetzung des Mikrobioms und in der Entwicklung von Pilzkontamination. So wurde in vielen Studien eine hohe Häufigkeit der Absonderung von Pilzen der Gattung *Malassezia furfur* und *Candida* auf der Haut bei AD nachgewiesen [7].

Aber diese pathogenetischen Mechanismen reichen jedoch nicht aus, um die Besonderheiten der allergischen Hautentzündung vollständig zu verstehen, die mit AD entstehen. Die Unfähigkeiten der Epidermis, eine Barrierefunktion bereitzustellen und die transkutane Penetration von Allergenen, Mikroorganismen und Feuchtigkeitsverlust zu verhindern sind offensichtlich durch die molekulargenetische Störungen verursacht, was die Bildung einer chronischen Hautentzündung bewirkt.

Auf der modernen Etappen ist Filaggrin (FLG) – ein Protein der Epidermis wichtig, was eine schützende Barriere sichert und den Verlust von Feuchtigkeit und das Eindringen von Allergenen und Mikroorganismen durch die Epidermis verhindert [8].

Es sollte angemerkt werden, dass der Polymorphismus im Filaggrin-Gen als ernsthafter genetischer Faktor für die Entwicklung nicht nur

von AD, sondern auch vom atopischen Marsch insgesamt angesehen wird [9]. Es wurden Daten über die Wirkung des Filaggrin-Polymorphismus auf die Bildung des Phänotyps von Asthma bei Kindern mit AD veröffentlicht [10].

Obwohl es mehr als 40 Mutationen bekannt sind, wurden heute nur Mutationen von Filaggrin-Gen 2282del4 und R501X detailliert erforscht, die in der Dritten Ekzone lokalisieren und spezifisch für verschiedene Populationen und Rassen sind [10]. Es ist bewiesen, dass es bei der europäischen Bevölkerung am häufigsten die Hauptmutationen im FLG-Gen R501X, 2282del4, S3247X, 3702delG, R2447X gibt [11].

In den Arbeiten von Weidinger und Co-Autoren wurde festgestellt, dass die wichtigsten Mutationen, die das Debüt und die Entwicklung von AD beeinflussen, werden R501X und 2282del4 [12] genannt, deren Rolle bei der Bildung anderer allergischer Erkrankungen bei Erwachsenen dargestellt wird [13]. Gleichzeitig wurde die Prävalenz und Vielfalt des FLG-Polymorphismus bei Kindern nicht ausreichend untersucht.

**Der Forschungszweck:** die Besonderheiten des klinischen Verlaufs der atopischen Dermatitis bei Kindern unter Bedingungen von den Filaggrin-assoziierten Störungen der epidermalen Barriere untersuchen.

#### **Materialien und Methoden der Forschung.**

111 Kinder von 3 bis 11 Jahren nahmen an der Studie teil. Vorab haben alle Patienten eine informierte Einwilligung zur Teilnahme an der Studie gegeben. Die Diagnose von AD wurde auf der Grundlage von Beschwerden, anamnestischen Daten, klinischer Untersuchung, Laborbefunden mit der Bestimmung des Niveaus von allgemeinen und spezifischen IgE, in Übereinstimmung mit lokalen und internationalen Protokollen und Leitlinien ausgestellt. Die Schwere von AD wurde nach der SCORAD-Skala bewertet. Das Material für die molekulare und genetische Analyse waren Bukkal epithelzellen.

Für die Bestimmung des morpho-funktionellen Hautzustandes wurde Methode von Corneometrie (portatives Corneometer Monaderm 98000 MONACO) angewendet, das den Grad der Hydratation der Epidermis bestimmen lässt. Entsprechend den

Eigenschaften des Geräts zeigt das Messergebnis von weniger als 30 auf der sehr trockenen Haut, von 30 bis 60 auf der trockenen Haut, über 60 auf der mit unterschiedlicher Stufe befeuchteten Haut an.

Die Einschätzung der Mikrobiozönose der Haut wurde nach den Ergebnissen der mikroskopischen und bakteriologischen Untersuchung des Hautabstriches durchgeführt.

Die Bestimmung des Einflusses von Polymorphismus im Filaggrin-Gen auf den Verlauf von AD wurde vergleichend die klinischen und Laborbefunde bei 51 Kindern mit dem vorhandenen Polymorphismus R501X und 2282del4 durchgeführt – die Hauptgruppe (A) und 60 Patienten ohne Polymorphismus – Vergleichsgruppe (B).

Die statistische Bearbeitung des Materials wurde mit Hilfe der Software Statistica 6 unter Verwendung parametrischer und nicht parametrischer Methoden zur Einschätzung der erhaltenen Ergebnisse durchgeführt. Es wurden die Richtigkeit der Verteilung der Merkmale für jede der erhaltenen Variationsreihen, die Durchschnittswerte jedes Merkmals, die untersucht wurden, Standardfehler und Abweichungen eingeschätzt. Die Zuverlässigkeit der Differenz zwischen den Werten der unabhängigen quantitativen Größen bei der richtigen Verteilung wurde mit Hilfe des Student-Kriteriums für unabhängige Größen bestimmt. Vergleichend die klinischen, Labor- und Instrumentalbefunde wurde die Bedeutung der Unterschiedsanzeichen in den Studiengruppen mit Hilfe des nicht parametrischen Pearson-Kriteriums  $\chi^2$  mit Verbesserung auf die Kontinuität. Bei der erwarteten Frequenz von 5 bis 9 wurde die Yates-Korrektur angewendet, bei der erwarteten Frequenz von weniger als 5 wurde das genaue Fisher-Kriterium verwendet. Die Unterschiede wurden bei  $p < 0,05$  als statistisch signifikant angesehen.

**Ergebnisse.** Nach den Ergebnissen der durchgeführten genetischen Untersuchung wurde festgestellt, dass Polymorphismus im Proteingen von Filaggrin bei 51 Kindern (45,9±6,98%) mit AD vorhanden ist. Die Mutation R501X traf bei 40 Kindern (78,4±5,76%), Polymorphismus 2282del4 bei 4 Patienten (7,8±3,76%,) kombinierte Variante R501X und

2282del4 bei 7 (13,7±4,81%) Patienten.

Signifikante Altersunterschiede in den Vergleichsgruppen wurden nicht festgestellt, jedoch war das Durchschnittsalter in Gruppe A mit  $7,2 \pm 2,1$  etwas größer als in Gruppe B mit  $6,5 \pm 2,1$  ( $P < 0,05$ ). Nach Geschlechtsmerkmalen waren die Gruppen vergleichbar: in der Gruppe A waren es 26 Jungen und 25 Mädchen, in der Gruppe B 28 Jungen und 32 Mädchen. In der Gruppe A wurde ein leichter Verlauf von AD bei 7 Kindern (13,7±4,81%), mittlerer Schwere - bei 16 (31,3±6,49%), schwerer - bei 28 (54,9±6,97%) Patienten diagnostiziert. In der Gruppe B waren die Ergebnisse signifikant unterschiedlich: so wurde der leichte Verlauf bei 20 Patienten (33,3±6,08%), der mittelschwere Verlauf bei 29 (48,3±6,45%) und der schwere Verlauf bei 11 (18,3±4,99%) Patienten festgestellt. Also, in der Gruppe B gibt es eine Tendenz, Patienten mit schwerem AD-Verlauf durch einen Anstieg des Prozentsatzes von Kindern mit leichtem Krankheitsverlauf zu reduzieren (Tabelle 1).

Bei der Einschätzung der Schwere von AD-Verlauf wurde festgestellt, dass in der Gruppe A der durchschnittliche Wert von SCORAD-Index  $52,8 \pm 7,5$  Punkte und in der Gruppe B -  $33,0 \pm 4,0$  ( $P < 0,05$ ); die Fläche der Läsion -  $52,1 \pm 13,2$  %; und  $19,5 \pm 10,2$  % ( $P < 0,001$ ) – dementsprechend. Die Schwere der objektiven klinischen Merkmale in der Gruppe A war  $10,2 \pm 1,7$  Punkte, in Gruppe B -  $7,2 \pm 1,3$  Punkte ( $P > 0,05$ ); die Intensität des Juckens in der Gruppe A -  $3,5 \pm 0,5$  Punkte, in der Gruppe B -  $2,3 \pm 1,1$  Punkte ( $P > 0,05$ ); Schlafstörungen in der Gruppe A -  $3,2 \pm 0,6$  Punkte und in der Gruppe B -  $1,8 \pm 0,6$  Punkte ( $P > 0,05$ ).

Bei der Untersuchung der Familiengeschichte in der Gruppe A ergab eine erbliche Belastung von  $60,8 \pm 6,84$  % der Kinder, in der Gruppe B – bei  $50 \pm 6,45$  % der Patienten ( $p > 0,05$ ). AD bei Angehörigen der ersten Verwandtschaftslinie in der Gruppe A wurde in  $72,6 \pm 6,25$  % identifiziert, wobei AD mindestens bei einem Elternteil in  $62,7 \pm 6,77$  % der Fälle und BA in  $41,2 \pm 6,89$  % aufgezeichnet wurde. Wie aus der vorgestellten Tabelle hervorgeht, steht in der Gruppe A das frühe Debüt von AD an. Nämlich bei 42 Kindern (82,4±5,33%) erschienen die ersten Symptome von AD bis 3 Monaten, und in der Gruppe B – nur bei 17 (28,3±5,82%). Bei den meisten Patienten der Gruppe A kam die Manifestation von AD für

Tabelle 1.

**Vergleichende Charakteristik des AD-Verlaufs berücksichtigend von Filaggrine-Polymorphismus.**

Anzeichen	Gruppe A n/%	Gruppe B n/%	Wert $\chi^2$
Debüt von AD bis zu 3 Monaten	42 (82,4% $\pm$ 5,33)	17 (28,3 $\pm$ 5,8)	33.235 p<0,001
Schwerer Verlauf von AD	28 (54,9 $\pm$ 7,0)	11 (18,4 $\pm$ 5,0)	16.176 p<0,001
Erhöhung des Niveaus von Gesamt-IgE	37 (72,5 $\pm$ 6,3)	45 (75,2 $\pm$ 5,6)	0.5523 p>0,05
Erhöhung des Eosinophilen-Niveaus	37 (72,5 $\pm$ 6,3)	37 (61,8 $\pm$ 6,3)	1.469 p>0,05
Sensibilisierung für Pilzallergenen	46 (90,2 $\pm$ 4,2)	21 (35,1 $\pm$ 6,2)	0.690 p>0,05
Sensibilisierung für <i>D. farinae</i>	37 (72,5 $\pm$ 6,3)	20 (33,4 $\pm$ 6,1)	16.971 p<0,05
Sensibilisierung für <i>D. pteronisin.</i>	37 (72,5 $\pm$ 6,3)	6 (10,0 $\pm$ 3,9)	45.447 p<0,05
Sensibilisierung für Hausstaub	33 (64,7 $\pm$ 6,7)	12 (20,0 $\pm$ 5,2)	13.891 p<0,05
Sensibilisierung für Pollenallergen	19 (37,2 $\pm$ 6,8)	19 (31,7 $\pm$ 6,0)	0.144 p>0,05
Sensibilisierung für bis 2 oder mehr Nahrungsmittelallergen	7 (13,7 $\pm$ 4,8)	30 (50,1 $\pm$ 6,5)	16.324 p<0,001
Verringerung der Hautfeuchtigkeit $\leq$ 45 Grade	51 (99,96 $\pm$ 0,44)	18 (30,1 $\pm$ 5,9)	0.000001 p<0,05
Reduzierung von Mikroorganismen- Kommensalen	37 72,6 $\pm$ 6,25	36 59,9 $\pm$ 6,33	1.928 p>0,05
Erhöhung der Pilzkontamination	16 31,4% $\pm$ 6,5	7 (11,7% $\pm$ 4,1)	6.517 p<0,05

einen Zeitraum von 3 bis 6 Monaten – 31 Kinder (51,6 $\pm$ 6,45%), älter als 6 Monate – bei 12 (20 $\pm$ 5,16%) Patienten. Diese Daten zeigen, dass die Altersbesonderheiten des klinischen AD-Verlaufs auf bestimmte Weise mit den morphofunktionellen Hautbesonderheiten verbunden sind, die für verschiedene Altersgruppen von Kindern charakteristisch sind. Beim Vergleich dieser Laborbefunde: Blut-Eosinophilie und Hyperglobulinämie E wurde keinen statistisch signifikanten Unterschied zwischen den Gruppen festgestellt (p>0,05).

Bei Corneometrie mit dem Untersuchungsziel von den morpho-funktionellen Hauteigenschaften wurde festgestellt, dass der durchschnittliche Feuchtigkeitswert der Epidermis in der Gruppe A signifikant niedriger als in Gruppe B (P<0,05) war, was eindeutig die schützenden Eigenschaften der Haut beeinflusste

(Tab. 1). Die inverse Beziehung zwischen Dimorphismus von Filaggrine und einer Verletzung des morph-funktionellen Hautzustands ( $r = -0.893$ ) wurde gefunden.

Die Verletzung der Barrierefunktion in Form von Veränderungen in der Mikrobiozönose der Haut durch die Verringerung der Mikroorganismen-Kommensalen und erhöhte Pilzkontamination bei der Untersuchung des Hautabstriches festgestellt: das Vorhandensein von Staphylokokken in der Gruppe A. Epidermidis wurde bei 14 Kindern (27,4 $\pm$ 6,2%), gleichzeitig in der Gruppe B - bei 24 Kindern (40,1 $\pm$ 6,3%) festgestellt. Die Pilz-Flora in auf Abstrichen wurde in der Gruppe A bei 16 Kindern (31,4 $\pm$ 6,5%) und in der Gruppe B - bei 7 Kindern (11,7 $\pm$ 4,1%) identifiziert.

Der genetisch deterministische Defekt der Hautbarriere als strukturelle Störungen von

Filaggrine, verantwortlich für die endgültige Differenzierung von Keratinozyten, führt zu einer Verletzung des Hautmikrobioms, und eine Verringerung der Mikroorganismen-Komensaen, zu denen *Staphylococcus epidermidis* gehört, was wiederum die Kolonisierung der Haut durch pathogene Mikroorganismen, insbesondere Pilze fördert.

#### Schlussfolgerungen:

1. Polymorphismus von Filaggrine-Protein wird bei 45,9% ± 6,98 Kindern mit AD festgestellt. Die Mutation R 501X wurde bei 78,4% der Kinder festgestellt, Polymorphismus 2282del4 bei 7,8% der Patienten, deren Kombination (R501X und 2282del4) bei 13,7% der Patienten.

2. Die Verletzung der funktionellen Eigenschaften der Epidermis unter FLG-Polymorphismus-Bedingungen manifestiert sich durch eine Abnahme der Höhe von Hautbefeuchtung ( $\chi^2_{0.000001}$ ), die Verletzung der Mikrobiözönose in Form einer Erhöhung der Pilzkontamination ( $\chi^2_{6.517}$ ).

3. Die Verletzung der Barriereigenschaften der Epidermis bei Kindern mit AD, die ein frühes Debüt mit sich bringt und den Verlauf der Krankheit belastet, trägt zur Erweiterung des Spektrums von Sensibilisierungsfeld bei.

**Perspektiven für weitere Forschung.** Die erhaltenen Ergebnisse demonstrieren die Wirkung des Dismorphysmus von FLG-Protein auf den klinischen Verlauf von AD bei Kindern und die Entwicklungsnotwendigkeit der therapeutischen Taktik unter Berücksichtigung des Zustands der Barriereigenschaften von Epidermis.

**Anmerkung.** In der Zahl ist die absolute Anzahl der Patienten angegeben. Im Nenner ist die relative Menge ( $M \pm m$ ) abgebildet.

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## AGE PECULIARITIES OF MORPHOFUNCTIONAL CHANGES OF TEMPORAL MUSCLE IN EXPERIMENTAL DIABETES MELLITUS

**Abstract.** *The changes in the structural components of the temporal muscle of 2-month-old white male rats in streptozotocin-induced diabetes mellitus (SDM) were investigated. It is established, that on the 14th day of SDM in the temporal muscle, stress-reactive changes in response to hyperglycemia are observed, which are manifested by spasm of arterioles, a decrease of the muscle fiber area by 1.4 times due to a decreased volume density of glycogen in 2.5 times. In the long term course of SDM (56 days) in temporal muscle compensatory-atrophic changes are noted. On the background of hyperglycemia and high levels of glycosylated hemoglobin, the development of diabetic microangiopathy was observed in vessels of hemomicrocirculatory bloodstream, which led to destructive changes in muscle fibers and nervous system of the temporal muscle. We found a decrease in muscle fiber area in 1.7 times and neuromuscular terminations in 3.2 times (in all cases  $p < 0.05$ ). However, it is worth noting the compensatory processes in the temporal muscle, which were manifested by the restoration of ultrastructure of myofibrils, increase of the volume density of glycogen and the formation of young mitochondria in sarcoplasm of muscle fibers. Appearance of young endotheliocytes in the vessels of hemomicrocirculatory bloodstream, that had electron-dense cytoplasm with a large number of micropinocytotic vesicles.*

**Key words:** *temporal muscle, muscle fiber, neuromuscular ending, streptozotocin-induced diabetes mellitus.*

**Introduction.** Over the past decade, there has been an increase in the incidence of endocrine diseases, in the structure of which the first place in the world belongs to diabetes mellitus (DM) [2, 15]. In various countries, the number of patients diagnosed with this disease ranges from 4-7% of the general population and tends to increase [2, 4]. Diabetes mellitus is the key medical and social problem of the public health care system in all countries of the world, which is associated with continuous increase of disease incidence, severe complications and high mortality rates, especially among the working-age population [16, 20, 21]. One of the DM complications is diabetic myopathy, which occurs in 88% of cases [5] and is often combined with other complications of diabetes mellitus such as: macro- and microangiopathy, cardiovascular diseases, nephropathy, retinopathy, neuropathy [4, 7, 8, 12, 18]. Diabetic myopathy is manifested by sharp pain and swelling. Usually the pathological

process involves the muscles of the lower extremities, particularly the thighs – 80% of cases and the lower leg in 20% [6, 19]. Palpable, painful mass is present in 34-44 % of patients, and fever occurs in about 10% of cases [5].

Taking the above into account, the **aim** of our investigation was to study the dynamics of histo-ultrastructural changes of temporal muscle of 2-month-old rats in the progression of streptozotocin-induced diabetes mellitus development.

**Material and methods.** The test material involved the temporal muscles of twenty 2-month-old white outbred male rats, which were divided into two groups: intact and experimental. Diabetes in experimental group animals was induced by a single intraperitoneal injection of streptozotocin (dissolved in 0.1M citrate buffer solution with pH 4.5) at a dose of 7mg per 100g of body mass. Glucose levels of experimental group animals were determined daily by taking blood

samples from the tail vein using test strips on an "Accu-Chec" (Germany) glucometer. Animals with blood glucose level higher than 13 mmol/l were selected for the study and material was collected during the 14<sup>th</sup> and 56<sup>th</sup> days of the experiment. The methods of investigation included: histological methods (hematoxylin and eosin staining, Masson's trichrome staining), histochemical (Shabadash's method of glycogen detection, Bilshovsky-Gross method of impregnation), biochemical and electron-microscopic ones.

All the procedures with test animals during the experiment were carried out in agreement with the regulations of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986), Council Directive 86/609/EEC (1986), the Law of Ukraine "On protection of animals from ill-treatment" of December 15, 2009 and orders of the Ministry of Health of Ukraine No. 690 dated September 23, 2009, No. 616 dated August 3, 2012.

Photographs of histological sections saved in tif format were used for morphometric studies. Morphometry was performed using ImageJ software version 1.47t. It became possible to determine the area of muscle fibers and their nuclei, as well as the area of neuromuscular endings. The profile area of arterioles, capillaries, venules, their walls and lumen were measured. Vohenvort index (VI) was measured in arterioles and capillaries using the corresponding formula[13]. Computerized data processing was performed using the STATISTICA package (StatSoft, Inc. (2010), STATISTICA (data analysis software system), version 10.

#### Results of investigation and their discussion.

On the 14<sup>th</sup> and 56<sup>th</sup> days of streptozotocin-induced DM development the levels of glucose and glycosylated hemoglobin increased to  $14.29 \pm 1.33$  mmol / l (control  $3.85 \pm 0.76$  mmol / l,  $p = 0.0159$ ) and  $15.42 \pm 1.33$  mmol / l (control  $3.26 \pm 0.84$  mmol / l,  $p = 0.0036$ ),  $6.46 \pm 0.14\%$  (control  $1.98 \pm 0.32\%$ ,  $p = 0.0023$ ) and  $9.74 \pm 0.17\%$  (control  $2.14 \pm 0.65\%$ ,  $p = 0.0023$ ), which indicates the development of decompensated diabetes mellitus.

On the 14<sup>th</sup> day of streptozotocin-induced DM development, we discovered a significant

decrease in the area of muscle fibers to  $365.43 \pm 46.95 \mu\text{m}^2$  (control –  $513.42 \pm 20.23 \mu\text{m}^2$ ,  $p = 0.0001$ ), whereas the area of their nuclei did not change significantly and made up  $12.49 \pm 2.35 \mu\text{m}^2$  (control –  $13.69 \pm 3.04 \mu\text{m}^2$ ,  $p = 0.2447$ ). In our opinion, such changes are associated with the decrease of glycogen inclusions in muscle fibers, which is confirmed by its unequal distribution: in some muscle fibers it is found only in the periphery, while in others it is absent (Fig. 1a). Statistical analysis showed a significant 2.5-fold decrease in the volume density of glycogen granules as compared to the control indices ( $p = 0.0017$ ). Histological specimens show arteriolar spasm whereupon the lumen of some of them assumes a slit-like shape (Fig. 1b). Inner elastic membrane resembles a dark helix and is not visualized along the entire perimeter of the vessel. However, the statistical studies show a significant decrease in the lumen of the arterioles due to a decrease in the area of their lumen (Table 1), whereas the area of the wall does not significantly change, leading to the increase of VI to  $424.65 \pm 43.54\%$  (control –  $358.44 \pm 58.09\%$ , ( $p=0.0001$ ) and points to the decrease in their blood flow capacity. We did not manage to detect significant morphometric changes on the part of metabolic and capacitance vessels (Table 1), but venous plethora was observed on histological preparations.

At this time of the experiment, the number of capillaries per  $0.1 \text{ mm}^2$  was not significantly different from the control values and made up  $96.3 \pm 4.01$  (control –  $99.2 \pm 2.49$ ,  $p = 0.0696$ ).

The study of preparations impregnated by the Bilshovsky-Gross method revealed thickening which formed along the myelinated nerve fibers (MNF) (Fig. 1c). The area of neuromuscular junctions was not significantly different from the control values and made up  $340.90 \pm 63.88 \mu\text{m}^2$  (control –  $337.11 \pm 35.71 \mu\text{m}^2$ ,  $p = 0.2885$ ).

At the ultrastructural level, mitochondria underwent the most pronounced changes in the muscle fibers of the temporal muscle on the 14<sup>th</sup> day of the SDM development. Their matrix is lucid, cristae become disorganized, somewhere destroyed. Separate muscle fibers have segmental contractures. An increase in the number of micropinocytotic vesicles in the cytoplasm of endothelial cells is observed in the links of hemo-

Table 1

**Morphometric changes of the hemomicrocirculatory bed in experimental diabetes mellitus**

HMCB Vessels	Group of Animals	Vessel Area	Lumen Area	Wall Area
14 <sup>th</sup> day				
arterioles	SDM	221.99±29.11*	46.92±11.81*	176.75±19.01
	control	280.68±49.50	61.57±10.14	219.10±42.76
capillaries	SDM	17.77±2.79	7.53±1.01	10.23±2.71
	control	15.42±3.30	7.32±1.65	8.09±2.16
venules	SDM	231.95±29.15	106.78±10.56	125.17±20.51
	control	230.14±35.29	102.75±10.65	127.40±27.56
56 <sup>th</sup> day				
arterioles	SDM	327.16±19.05 <sup>#</sup>	32.75±7.10*	198.41±14.51* <sup>#</sup>
	control	315.80±28.63	72.85±15.86	242.95±22.16
capillaries	SDM	16.15±5.44	3.85±1.43* <sup>#</sup>	12.30±5.41* <sup>#</sup>
	control	15.65±3.21	7.69±1.57	7.96±2.24
venules	SDM	275.45±33.85 <sup>#</sup>	105.19±33.40*	170.25±35.69* <sup>#</sup>
	control	308.25±40.60	149.27±24.82	158.97±28.93

Notes:

- 1) \* $p < 0.05$  – the probability indices as compared to the control;
- 2) <sup>#</sup> $p < 0.05$  – the probability indices as compared to the previous term of experiment.

microcirculatory bed, indicating an increase in transendothelial transport. In the axoplasm of neuromuscular synapses, the mitochondrial matrix is lucid and the number of synaptic vesicles is increased by 12.8% as compared to the control indices ( $p = 0.6547$ ).

Marking: 1 - glycogen granules, 2 – spasm of arterioli, 3 - normal arterioli, 4 - arterio-venular anastomosis, 5 – adhesion of erythrocyte, 6 - terminal axon branches, 7 - nuclei of terminal

neuromuscles, 8 – swelling of endomysium, 9 - reduction of axon spouting in neuromuscular endings.

On the 56<sup>th</sup> day of SDM course we have observed a significant increase in the area of muscle fibers, up to  $444.09 \pm 58.85 \mu\text{m}^2$  as compared to the previous experimental period ( $p < 0.0001$ ), though they remain below the control parameters ( $p < 0.0001$ ). The area of nuclei increased to  $15.79 \pm 2.67 \mu\text{m}^2$  as compared to the

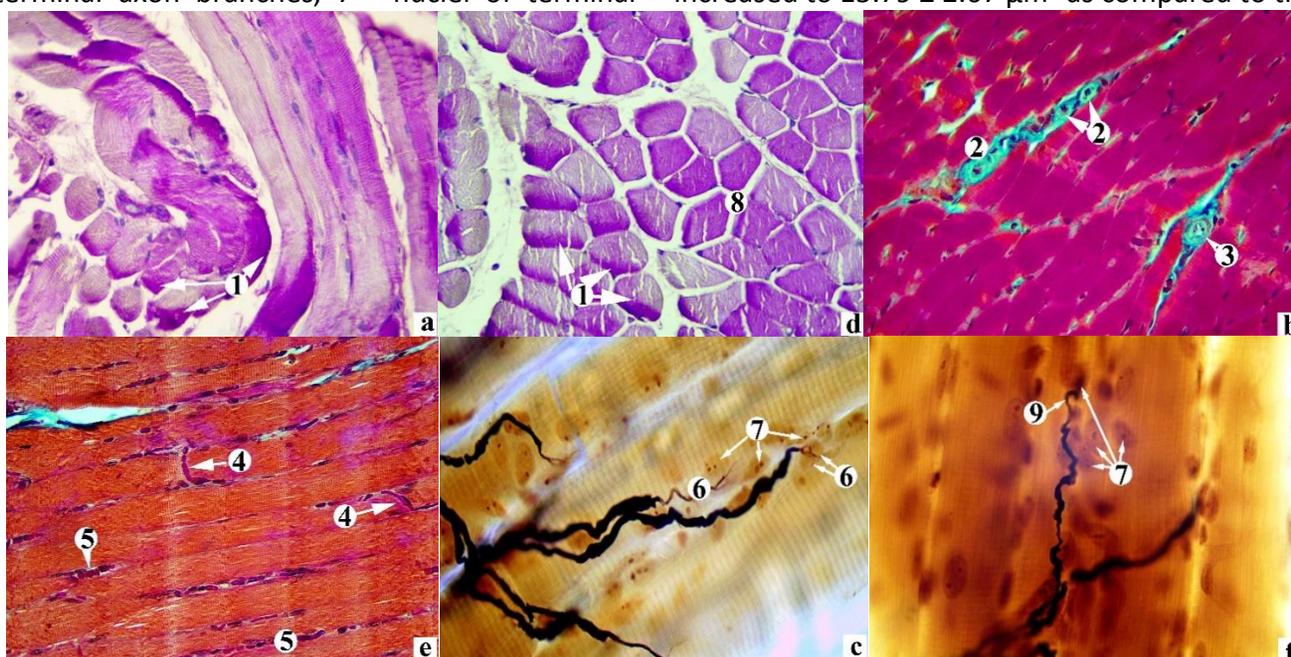


Fig. 1. Histostructural changes of temporal muscle of 2-month-old rats on the 14th day (a-c) and 56th day (d-f) of streptozotocin diabetes mellitus. Coloring: Shabadash (a, d), Masson trichrome (b, e), Bielschowski-Gross impregnation (c, f). Microphotographs. Magnification: a, b, d, e) x400; c, f) x1000.

previous observation period ( $p = 0.0098$ ), but did not differ significantly from the control parameters (control –  $14.52 \pm 4.27 \mu\text{m}^2$ ,  $p = 0.4093$ ). Histological preparations show swelling of endo- and perimysium (Fig. 1d), defibrillation and focal lysis of individual muscle fibers and their histolymphocytic infiltration, which may indicate the development of aseptic myositis. As compared to the previous experimental period, muscle fibers are moderately and equally filled with glycogen granules (Fig. 1d), indicating partial compensation of metabolic changes in the test muscle.

Multiple nummular erythrocytic sludges, aggregation of erythrocytes and thrombocytes to the luminal endothelial surface were discovered in the hemomicrocirculatory bed. The wall area of all microvessels (Table 1) increases, which, when narrowing the lumen of arterioles and capillaries, leads to an increase in their VI to  $1057.50 \pm 72.09\%$  (control –  $347.69 \pm 76.87\%$ ,  $p = 0.0001$ ) and  $377.49 \pm 51.16\%$  (control –  $105.75 \pm 28.94\%$ ,  $p = 0.0001$ ), indicating significant decrease in their blood flow capacity. At the same time the area of venules significantly increases (Table. 1). Such restructuring of microvessels points to the opening of arterio-venular anastomoses (Fig. 1e), which has a compensatory-protective value, since it provides shunting blood into the venous bed. Such changes in angioarchitectonics of the temporal muscle lead to a decrease in the number of hemocapillaries per  $0.1 \text{ mm}^2$  to  $58.8 \pm 8.38$  as compared to the previous experiment period and control period (in all cases  $p < 0.05$ ).

Histological preparations impregnated by the Bilshovsky-Gross method show increased number and size of varices of the preterminal parts of MNF, decrease in axon sprouting (Fig. 1f), which is confirmed by the morphometric findings, namely: the area of neuromuscular connections decreases to  $186.32 \pm 34.26 \mu\text{m}^2$  (control –  $511.35 \pm 66.24 \mu\text{m}^2$ ,  $p = 0.00005$ ). The heterogeneity of the muscle fiber structure was observed on the ultrastructural level. In some cases, we observed karyorrhexis, lysis of individual myofibrils, expansion of the structural components of the sarcoplasmic reticulum, destruction of mitochondrial cristae with subsequent vacuolation, presence of myelin-like inclusions in mitochondria (Fig. 2 a). While in other muscle

fibers, we observed intracellular regenerative processes, which were manifested by: the preserved ultrastructure of myofibrils, the presence of glycogen granules in sarcoplasm, the formation of young mitochondria with electron-dense matrix and fuzzily differentiated cristae.

Electron microscopic examination revealed stratification of the lamella of the MNF myelin sheath, widening of the periaxonal space (Fig. 2c). Axoplasm was of low electron density in terminals of axons which form neuromuscular synapses. Here we have found mitochondria with lucid matrix, small number of neurofilaments, microtubules and synaptic vesicles. Post-synaptic folds are disorganized, sometimes shortened and destroyed in neuromuscular synapses (Fig. 2d).

In the vessels of the hemomicrocirculatory bed, the most pronounced changes were observed in endothelial cells. Their cytoplasm was electron-dense with a large number of micropinocytotic vesicles (Fig. 2 e-f). The luminal surface of the plasmolemma forms long and short fingerlike protrusions in the lumen of the microcirculation vessels, with subsequent formation of microclasmatosis, which, along with hemoreologic disorders, impairs blood supply to the muscle.

Basal membrane of the capillaries undergoes marked changes. It loses its three-layer structure, considerably thickens due to its proliferation in the form of separate plates (Fig. 2 f), which is one of the markers of diabetic microangiopathy.

Marking: 1 – destructively altered mitochondria, 2 – young mitochondria, 3 – glycogen granules, 4 – myofibril lysis, 5 – stratification of myelin sheath, 6 - disorganization and destruction of synaptic folds in neuromuscular synapses, 7 – finger-shaped protrusions of the luminal surface of the plasmolemma of endothelial cells, 8 – thickening of the inner elastic membrane, 9 – multilayered basal membrane.

**Discussion.** During early stages of SDM course (14<sup>th</sup> day), we have observed a decrease in MF area by 28.8%, which, in our opinion, was associated with the decrease in their glycogen content. Such changes are associated with the increase of contra-insular hormones, particularly cortisol, in blood in response to hyperglycemia,

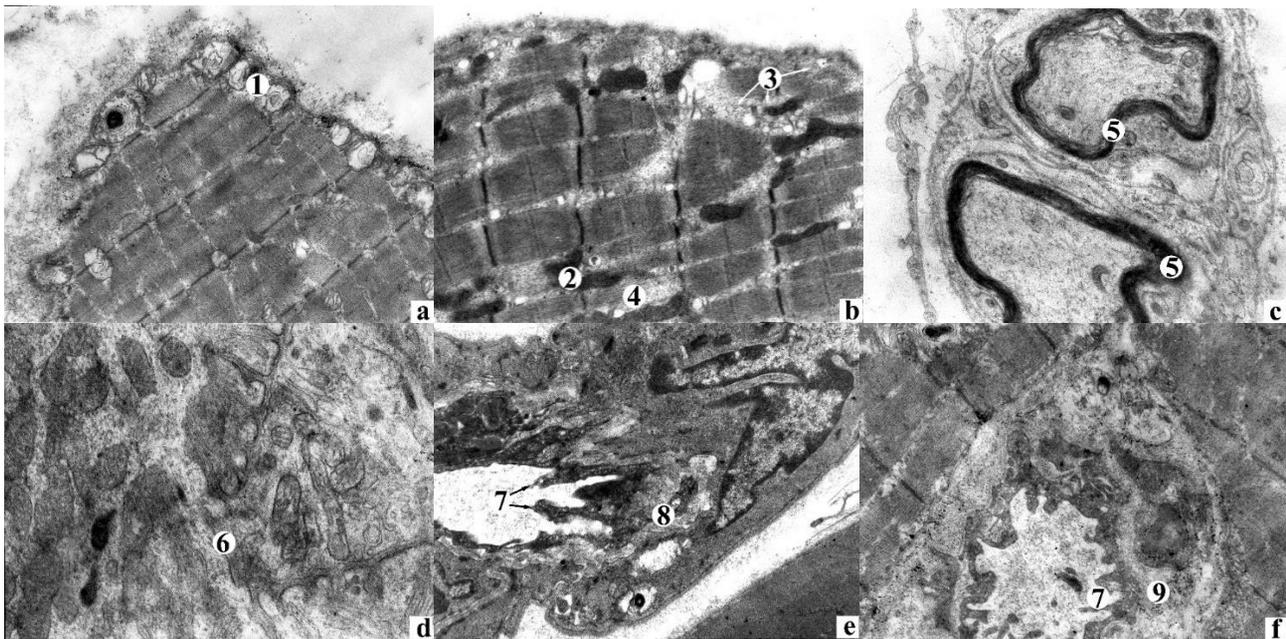


Fig. 2. Ultrastructural changes of muscle fibers (a, b), myelin nerve fibers (c), neuromuscular synapses (d), arterioles (e), capillaries (f) on the 56<sup>th</sup> day of the course of SDM. Magnification: a, e, f) x8000; b, c) x9600, d) x16000.

[15, 16], as they promote gluconeogenesis in insulin deficiency. It is worth noting that the hyperproduction of contra-insular hormones in DM is one of the pathogenic links in the development of diabetic angiopathies [10, 11, 18]. At the same time, some authors note high levels of cortisol in the early stages of SDM development [15], which, according to our research, leads to the spasm of afferent vessels and is accompanied by a significant decrease in their lumen by 1.8 times, resulting in the increase in VI by 1.7 times and indicates a decrease in the blood flow capacity of these microvessels. Disturbances in the microcirculatory system lead to hypoxic damage to the muscle fibers, which, according to our research and the studies of other authors, manifest themselves as segmental contractions of myofibrils and destructive mitochondrial changes [20, 21].

With the course of the experiment (56<sup>th</sup> day of SDM) we have observed the development of diabetic microangiopathy in temporal muscles, which is principally manifested as hemoreologic disorders, namely: erythrocytic sludge, adhesion of erythrocytes and platelets, microclasmotosis. Most researchers believe that such blood flow changes are associated with high levels of glycosylated hemoglobin, which leads to the change in the shape of erythrocytes (their S-surface charge). Sludge and agglutination of erythrocytes lead to the formation of

microthrombi, which result in local circulatory and hemic hypoxia and activate the molecular mechanisms which cause damage to the plasmolemma of endothelial cells [1, 10, 12]. The damage of the latter is also influenced by low levels of vasodilators (nitric oxide and prostacyclin) as DM is associated with the development of ketoacidosis and glycosylation of the N-terminal ends of transmembrane proteins [11]. Sorbitol pathway of glucose metabolism is another factor in the destruction of endothelium in diabetes, as it is associated with the activation of aldose reductase with subsequent sorbitol accumulation in endothelial cells, leading to osmotic edema and destruction of the latter [12, 14]. Hyperglycemia, due to increased activity of glucosyltransferase [1], promotes increased synthesis of glycoproteins in the basal membrane, which, according to our studies, leads to its thickening and proliferation in the form of separate plates and is one of the characteristic signs of diabetic microangiopathy.

Some authors [20] state that in diabetes the function of synaptic apparatus of skeletal muscle is impaired. Autoantibodies to the voltage-gated Ca<sup>2+</sup> channels at the presynaptic membrane of neuromuscular synapses are considered to be the leading damaging agents. It is a known fact that their effective functioning requires the sufficient amount of energy-related material. However, insulin deficiency in diabetes results in acute

glucose deficiency in neurons and muscle fibers [3], impeding synthesis and isolation of synaptic acetylcholine mediators from axon terminals. Another mechanism of damage to neuromuscular synapses is hypoxia due to the development of diabetic microangiopathy. In this case, the cytoplasm of neurolemocytes is overloaded with a large number of vesicles of different size [20], and the myelin sheath becomes stratified [9], which is clearly observed in our investigations. On the one hand, it may serve as a morphological substrate for the disturbance of oxidative metabolism in SDM, while on the other hand, it explains the hypotrophic changes in the temporal muscle due to impaired energy supply, delayed axonal transport, decreased number of neuromediators and destructive mitochondrial changes [9, 20]. Our studies show that muscle fiber area was 1.7 times smaller than the control indices. However, we should also note the compensatory processes in temporal muscle of immature rats, which were manifested by the following intracellular regenerative phenomena: the restoration of ultrastructure of myofibrils, increase in the number of glycogen granules in sarcoplasm, formation of young mitochondria with electron-dense matrix and obscurely differentiated cristae. Young endotheliocytes with electron-dense cytoplasm and large number of micropinocytotic vesicles were observed in micro-hemo-vessels [17].

**Conclusions.** Thus, in the early stages of SDM development (14<sup>th</sup> day), we have observed stress-reactive changes in the temporal muscle in response to hyperglycemia, which were manifested by: the spasm of the arterial link of the hemomicrocirculatory bed, decrease in the area of muscle fibers due to the reduction in volume density of glycogen.

Compensatory-atrophic changes of temporal muscle were observed during the later stages of SDM course (56-70<sup>th</sup> days). Against the background of hyperglycemia and high levels of glycosylated hemoglobin, the development of diabetic microangiopathy was observed in the hemomicrocirculatory bed resulting in destructive changes to the muscle fibers and nerve apparatus of the temporal muscle.

However, we should also point to the compensatory processes in the temporal muscle

of juvenile rats, which were manifested by intracellular regenerative phenomena in muscle fibers and the appearance of young endothelial cells in the micro-hemo-vessels.

**Directions for further research** consist in comprehensive study of the patterns of changes in muscle fibers, hemomicrocirculatory bed and neuromuscular endings of the temporal muscle with SDM and its correction with various antidiabetic medications.

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## ULTRASTRUCTURE OF NEURONS OF SUPRAHIASMATIC NUCLEI OF RAT HYPOTHALAMUS UNDER CONDITIONS OF PHOTOPERIOD MODIFICATIONS

**Abstract.** *Submicroscopic organization of pacemaker cells of the ventrolateral region of the suprachiasmatic nuclei of the anterior hypothalamus in rats was studied. Under the standard LD illumination regime (12.00 – 12.00), the ultrastructure of pacemaker neurons indicates a decrease in their functional activity in the light, and an increase in the darker period of the day. Continuous light stress LL (24.00L:00D) leads to a significant desynchronization of the circadian pacemaker and inhibition of its activity during the observation period. Modeling of the hypothyroidism of the pineal gland causes destructive changes in the components of the studied structures, more pronounced at 2 a.m.*

**Key words:** *hypothalamic suprachiasmatic nuclei, permanent illumination*

**Introduction.** Photoperiod is the main timing factor for the synchronization of the rhythms of somatic and visceral functions, as well as the coordination and modulation of the mechanisms of adaptation of the organism to the influence of various factors [2,5]. An oscillator that controls mammals most of the rhythms, in particular, circadian (rituals) rhythms, localized in the pacemaker neurons of the ventrolateral unit of the suprachiasmatic nucleus (SCN) of the hypothalamus [5,8]. Light information is perceived by the retina, is transmitted to the retinogipotalamic tract to the SCN and, later, through the intermediary structures, enters the epiphysis cerebri (pineal gland) [9]. Secretory cells of the gland - pinealocytes synthesized the main neurohormon melatonin [9]. Among the wide range of hormone effects, chrono-regulating is crucial [7]. Physiological control of the function of the pineal gland of mammals is carried out to a large extent by the mode of illumination [4]. In the light melatonin products are suppressed by the gland. Continuous darkness stimulates the

secretion of the epiphyseal hormone, and thus causes changes in the activity of the circadian pacemaker, which is reflected on the ultrastructure level [8]. The aim of this work is to elucidate the submicroscopic rearrangements of the neurosecretory cells of the ventrolateral region of the suprachiasmatic nuclei of the hypothalamus in different diurnal periods under constant illumination.

**Material and Methods.** Experiments were carried out on 24 adult mongrel male albino rats weighing 150 to 180 g. Animals were kept under standard vivarium conditions, at the controlled temperature and air humidity; free access to water and food was provided. The purpose of the study can be considered the pacemaker cells of the ventrolateral unit of the SCN of the hypothalamus.

The animals were divided into two groups; in each of the latter collection of biomaterial was carried out at 2 p.m. and at 2 a.m. The period of the experiment depended on different functional activity of the pineal gland in the specified time of

the day.

Intact animals of the 1<sup>st</sup> group were kept for 14 days under conditions of normal illumination periodicity (group LD, illumination (50 lx in the cages) was provided from 8.00 until 20.00 with luminescent lamps). Rats of the 2<sup>nd</sup> group were kept for 14 days under conditions of continuous illumination (group LL, induction of the epiphyseal hypofunction).

On the next day after termination of the 14-day-long conditioning period at 2 p.m. and 8 p.m., animals were decapitated under Ethanal anesthesia (40 mg/kg i.p.).

For the pacemaker neurons of the ventrolateral unit of the SCN of the hypothalamus electron microscopy mapping the samples were collected in conformity with generally accepted rules. The pacemaker neurons were identified in slices of the hypothalamus using electron microscopy. 1-1.5 thick slice of the ventrolateral unit of the SCN of the hypothalamus was dissected. First, the slice was incubated in 2.5% solution of glutaraldehyde in Millonig's buffer (pH 7.2-7.4). Then the fixed material was incubated in buffer solution and washed off for 20-30 min. After this, the post-fixation of the material for 60 min was performed, using 1% solution of osmium tetroxide in Millonig's buffer. After a standard procedure of dehydration in ethanol and acetone and immersion in a mixture of epoxy resins was carried out. A weak red illumination (2 lx) was provided at night, which had little effect on the melatonin biosynthesis with the pineal gland [1] were carried out in accordance with the main requirements of the Decree of The First Regional Meeting of National Bioethics Committees (NBC) "Ethical Principles and Guidelines for Experiments on Animals" (2001), the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes of 18 March 1986, the EU Council Directive 86/609/EEC of 24 November 1986 and the Ministry of Health of Ukraine Directive No. 690 of 23 September 2009, No. 944 of 14 December 2009, No. 616 dated 03 August 2012 and the laws of Ukraine.

**Results and their discussion.** Submicroscopic analysis of the SCN of the hypothalamus of the intact animals at 2 p.m. showed that most of the neurosecretory cells have reduced irregularly shaped nuclei with shallow invaginations of the carrier. The karioplasma has lumps of chromatin and a dense osmophilic nucleolus. The neuroplasma takes up small volume densely filled with a small lumen of the granular endoplasmic reticulum

and Golgi complex cisternae with a few vacuoles and bubbles. The light small matrices and somehow modified mitochondria crystals are observed there. In the neuroplasm of such neurosecretory cells there is a small amount of hormonal granules. The indicated submicroscopic organization of neurosecretory cells reflects a low functional activity.

The study of the ultrastructural organization of the hypothalamic scintillation in intact animals at 2 a.m. revealed that the neurosecretory cells frequently have nuclei with significantly uneven nuclear membrane and deep invaginations, therefore increasing the area of an interaction between the nucleus and the cytoplasm. The euchromatin predominates in the karioplasma; only small osmophilic lumps of heterochromatin are noticeable. In most nuclei, large nucleoli and many ribosomal granules are visible. The nuclear envelope has numerous nuclear pores.

Most neurosecretory cells of the neuroplasm are occupied with long tubules of granular endoplasmic reticulum with a narrow lumen; and the organelle membranes contain ribosomes. The Golgi bodies (dictyosomes) are characteristically flattened cisternae with perinuclear arrangement having moderate quantity of vacuoles and bubbles filled with osmophilic contents. These are forming neurohormonal granules. The electron microscope revealed a group (pair) arrangement of neurosecretory cells in some fields of view. Their ultrastructure is similar to the one described above. In the axon leaving this cell more intensely osmophilic small hormonal granules are found. Such a pattern indicates the active functional state of the pacemaker cells of the SCN.

The SCN of the hypothalamus ultrastructural organization of the animals kept for 1 week under conditions of light stimulation at 2 p.m. was reflected by the presence of radiant neurosecretory cells with dense round core. Their karioplasma usually contains euchromatin and sites of heterochromatin (Fig. 1). In the neuroplasm of the SCN neurons, destructive changes of organelles are identified. Fragmentation and expansion of the tubules of the granular endoplasmic reticulum and Golgi complex cisternae occurs with the vacuoles formation. The mitochondria destruction is accompanied by focal illumination of their matrix. In such neurosecretory cells the content of hormonal granules is insignificant. There are also dark neurosecretory cells which usually have pyknotic nuclei with osmophilic karioplasma and

nuclear membrane invagination. Their electron-density neuroplasm has destructively altered organelles and few horizontal granules (Fig. 1).

For 14 days under conditions of 24 h illumination at 2 a.m. the neurosecretory cells having light nuclei with uneven contours and mild pores were identified submicroscopically. The nuclear membrane contains very few ribosomal granules and occasionally nucleoli. The neuroplasma has a high electron density and "fuzzy" membrane organelle. The focal expansion of the granular endoplasmic reticulum tubules with the formation of vacuolic structures is found. Part of the mitochondria has a bright matrix and reduced crystals with detached hormone granules (Fig. 2). The ultrastructural state described above indicates a decrease in the functional activity of structures with elements of destruction.

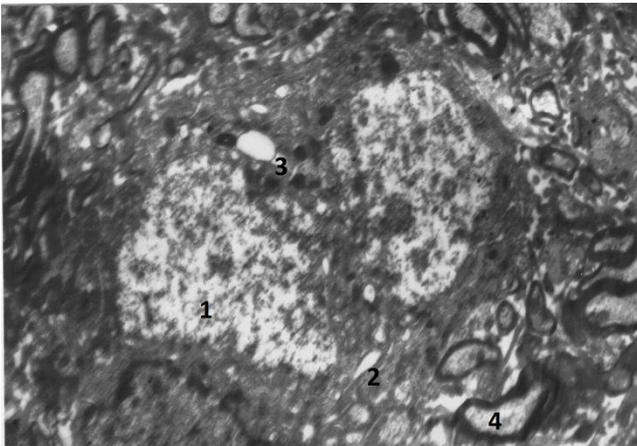


Fig. 1. The submicroscopic organization of the pacemaker cells of the ventrolateral unit of the SCN of the rat anterior hypothalamus at 2 p.m. under constant illumination conditions: 1 - nuclear membrane of dark neurocyte invaginations; 2 - dilated tubules of the granular endoplasmic reticulum; 3 - Golgi complex destruction x 7 000.

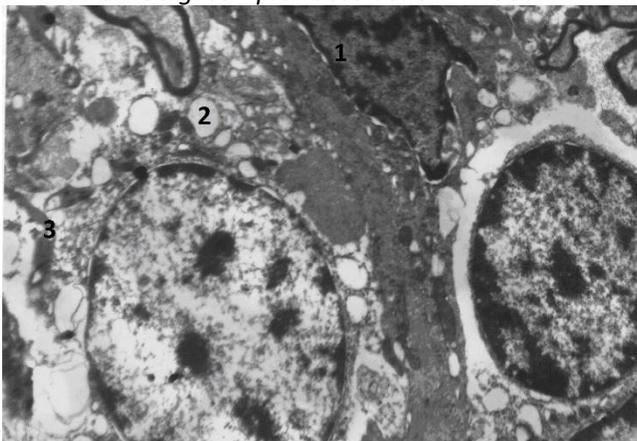


Fig. 2. The changes in the ultrastructural organization of neuronsecretory cells of the ventrolateral unit of the SCN of the rat anterior hypothalamus at 2 a.m. under the light stimulation: 1 - euchromatin nucleus; 2 - destroyed organelles; 3 - neurosecretory granules; 4 - myelinated nerve fibers. x 8 000.

Thus, the ultramicroscopic changes found in the pacemaker cells of the SCN of the hypothalamus can be considered as a reflection of desynchronization. According to the references, prolonged permanent illumination causes hypofunction of the pineal gland, and, accordingly, a decrease of melatonin production. Inhibition of a synthesis of this natural chronobiotic is the main cause of the functional disorganization of the pacemaker cells of the ventrolateral unit of the SCN of the hypothalamus.

Under the standard illumination regime the submicroscopic organization of pacemaker cells of the ventrolateral unit of the SCN of the rat anterior hypothalamus indicates a decrease in the functional activity of the neurons in the light cycle and its growth in the dark cycle. A long-term light stress leads to significant desynchronization of circadian pacemaker and inhibition of its activity during the follow-up period. In pineal gland hypofunction modeling the destructive changes in the components of the studied structures are more pronounced at 2 a.m.

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## **REGULARITIES OF MORPHOGENESIS OF INTERNAL FEMALE GENITAL ORGANS IN THE PERINATAL PERIOD OF ONTOGENESIS**

**Abstract.** *The thesis deals with determination of chronologic succession regularities in perinatal morphogenesis and formation of topographic-anatomical interrelations of the internal female reproductive organs. Peculiarities of a typical and variant anatomy of the uterus, vagina, ovaries and uterine tubes are studied on 160 specimens of fetuses and newborns applying a complex of morphological methods of examination: macroscopic, common and thin section, microscopic, vessel injections, making topographic-anatomical sections, radiological, computed tomography, three-dimensional computed reconstruction, morphometric and statistical. As the result of morphometric examination of the internal female reproductive organs at every stage of the perinatal period appropriate variation series are formed. The distribution for them was evaluated, arithmetic mean with standard quadratic deviation and percentile scale of values were calculated. Reliability of difference between independent quantitative values was determined by means of Mann-Whitney U-criterion. Spearman statistical test was applied to analyze correlations of the results obtained. By means of the applied methods of examination combined, the individual and age anatomical variability and spatial-temporal perinatal transformations of the internal female reproductive organs with the following determination of critical periods were determined for the first time. It is of great importance for finding morphological preconditions promoting occurrence of congenital developmental defects (CDD). Peculiarities of the structural organization of the internal female reproductive organs in fetuses of different term groups are determined.*

**Key words:** *ovaries, uterus, uterine tube, fetus, anatomy.*

New, unknown earlier data concerning chronological succession of topographic-anatomical interrelations of the internal female reproductive organs between themselves and adjacent organs and structures during the perinatal period of human ontogenesis were obtained by means of current and classical methods of investigation. Perinatal normative anatomical standards of the internal female reproductive organs are determined for the first time. On the basis of the results obtained the stages of a definite structure formation of the internal female reproductive organs are determined in dynamics of their development as well as the mechanisms of occurrence of their structural variants and possible CDD. It will enable to understand better the course of pathological processes, prevent possible complications, and form an anatomical basis for development of new methods of their surgical correction in fetuses and neonates [1-6].

**The purpose of the study** - to determine for the first time the succession of formation of the uterus, ovaries, uterine tubes and vagina during the fetal and early neonatal periods of human ontogenesis.

**Materials and methods:** A comprehensive statistical analysis of the morphometric parameters of the internal female reproductive organs between the objects of the study remote in time was conducted for the first time (I group – 35 specimens of fetuses deceased during 2017-2019; II group – 105 specimens of fetuses from the Museum of M.G.Turkevych Department of Anatomy, Clinical Anatomy and Operative Surgery, Bukovinian State Medical University, collected in the period 1995-2000). Differences of their fetal anatomy under a probable influence of constantly changing environmental conditions were found. For the first time differences in the structure of the internal female reproductive organs in fetuses of various terms between the

groups of morphological investigation remote in time were found.

New, unknown earlier data concerning chronological succession of topographic-anatomical interrelations of the internal female reproductive organs between themselves and adjacent organs and structures during the perinatal period of human ontogenesis were obtained by means of current and classical methods of investigation. Perinatal normative anatomical standards of the internal female reproductive organs are determined for the first time. On the basis of the results obtained the stages of a definite structure formation of the internal female reproductive organs are determined in dynamics of their development as well as the mechanisms of occurrence of their structural variants and possible CDD. It will enable to understand better the course of pathological processes, prevent possible complications, and form an anatomical basis for development of new methods of their surgical correction in fetuses and neonates.

**Results.** Normative fetal parameters of the internal female reproductive organs and the periods of their slow and accelerated development were determined on the basis of the morphometric and statistical analyses conducted. Possible variants in the structure and topography of the ovaries, uterus, vagina and uterine tubes were first substantiated. New scientifically substantiated data contribute considerably current views concerning the regularities of ontogenetic chronology of the perinatal development of the internal female reproductive organs.

Perinatal changes of the uterine shape are observed, a certain shape of the uterine fundus at every stage of the perinatal development is determined. The relief of the uterine fundus is confirmed to differ by its greatest variability. It can be vallecuate, tuberculous, flat and convex. Physiological disappearance of the channel on the uterus is followed. It is confirmed by the determined reliable reverse correlations of average force between the width of the uterine fundus which parameters range from  $6,0 \pm 0,21$  mm to  $6,4 \pm 1,60$  mm, and parietal-calcaneal length (PCL) of the fetus.

Canalization of the vagina in the caudal-cranial

direction is observed till the end of the 5th month of the intrauterine development. Variability of the vaginal cavity shape in human fetuses of different terms is determined. For example, in 5-6-month fetuses the following variants of shape in the upper and middle thirds of the vagina are found: oval, elongated-oval, stellate; the lower third is mostly of H-like and C-like shapes.

Macroscopic and microscopic methods of examination confirmed transformation of an elongated triangle shape of the ovary (at the beginning of the perinatal period of ontogenesis) to an oval one (in 8-10-month fetuses and neonates), and their transitional shapes are described: flattened, segmental and fusiform (spindle-shaped). Peculiarities of the ovarian topography for every age group are found. At the beginning of the fetal period of ontogenesis the ovaries are usually in the ascending position (86,6 %). Thus, an ascending position of both ovaries was found in 48,3 % of the examined 4-6-month fetuses, including the right ovary – 15 % of cases and the left ovary – 23,3 % of cases. Beginning with the 6th month, fetal ovaries become of a horizontal or descending position. At the end of the fetal period a horizontal or descending position of both ovaries was found in 33,3 % of cases including the right ovary – 16,6 % and the left one – 11,6 % of cases. At the same time, in 38,5 % of the examined 8-10-month fetuses both ovaries were found to be in the uterine-rectal depression.

During caudal transition of the ovaries their morphometric parameters increase relatively slow (5-8-month fetuses), which is evidenced by the determined reliable correlations of an average force between the ovarian width and PCL of the fetus. Morphometric parameters of the right ovary width in the fetuses during this term of development range from  $3,4 \pm 0,82$  mm to  $4,1 \pm 0,64$  mm, and the left one – from  $3,2 \pm 0,59$  mm to  $3,7 \pm 0,25$  mm. During the fetal period certain changes in the microscopic organization of the ovarian parenchyma are found which is manifested in gradual migration of the medullary substance and cortical cords from the center with their gradual disappearance in the portal portion in 8-month fetuses and their simultaneous substitution by the blood vessels. The differences found in the anatomical structure of the ovaries in

fetuses of various terms differ totally from those in the postnatal period of human ontogenesis. Considering prevailing triangular shape of the ovaries in 4-6-month fetuses (87 % of cases), and the fact that one of its borders is directed to the uterine tube and is the point of attachment of its mesentery, we suggest to term it “tubular border” of the ovary. The border and surface passing in the caudal direction from the uterine tube and tubular border should be termed the lower border and ovarian surface. The border and surface directed to the cranial part should be termed upper ones. The surface located opposite to the tubular border of the ovary should be reasonably termed anterior one. Therefore, the ovary with a triangle shape might have mesenteric or tubular border and two free borders – upper and lower one, and the surface determined opposite to the tubular border and located between the free borders might be termed the anterior one.

For the first time, morphometric parameters of the internal female reproductive organs in the group of fetuses, remote in time, were analyzed. The length of the left ovary of present 7-month fetuses ( $9,4 \pm 1,06$  mm) and the length of the right ovary of present 8-month fetuses ( $12,9 \pm 1,23$  mm) were evidenced to be reliably shorter ( $p < 0,05$ ) than that of the archival specimens ( $11,6 \pm 1,87$  mm and  $14,7 \pm 1,44$  mm respectively). The width of the left ovary of present 4-month fetuses ( $0,9 \pm 0,06$  mm) appeared to be reliably shorter ( $p < 0,05$ ) than that of the archival specimens ( $1,2 \pm 0,22$  mm). The thickness of the right ovary of present 7 and 10-month fetuses ( $1,8 \pm 0,25$  mm and  $3,8 \pm 0,36$  mm) appeared to be reliably smaller than that in the appropriate groups of the archival specimens ( $2,3 \pm 0,59$  mm and  $4,6 \pm 0,8$  mm respectively). The thickness of the left ovary of present fetuses at the end of the perinatal period is marked to be reliably smaller ( $p < 0,05$ ) than that of the archival specimens ( $3,3 \pm 0,36$  mm and  $4,2 \pm 0,83$  mm respectively).

Changes of the structural organization of the uterine tubes were found for the first time, and the dynamics of formation of their shape and topography during the fetal period of development was observed. Stages of formation of the uterine tube convolution during the perinatal period of human ontogenesis are described. Changes of their position from the

ascending to descending one are confirmed to be associated with a relative delay in growth of their morphometric parameters, which is evidenced by the reliable reverse correlations of an average force found ( $r = -0,16$  and  $-0,32$ ) between the length of the uterine tubes and fetal PCL. Morphometric parameters of the right uterine tube length in the period from 7 to 10 months of the intrauterine development were found to increase from  $14,5 \pm 3,77$  mm to  $22,4 \pm 3,38$  mm, and the left uterine tube – from  $12,9 \pm 3,78$  mm to  $21,0 \pm 3,38$  mm. The stages of the uterine tube formation are determined – from curved (at the beginning of the fetal period), zigzag and spiraled (in the middle of the fetal period) to the curved spiraled shape (at the end of the fetal period and in neonates). The regularities found are evidenced by the analysis of morphometric parameters of the uterine tubes by means of Mann-Whitney U-criterion, and they are indicative of a reliable difference in their parameters ( $p < 0,05$ ) in 8-month fetuses ( $16,0 \pm 0,79$  mm – of the right uterine tube,  $14,9 \pm 1,34$  mm – of the left one) and in 9-month fetuses ( $22,6 \pm 1,51$  mm – of the right uterine tube,  $20,8 \pm 1,83$  mm – of the left one).

On the basis of regularities found in the morphogenesis of the internal female reproductive organs their critical periods and morphological preconditions of occurring variant and congenital developmental defects were determined. Critical periods coincide with the period of an intensive enlargement of morphometric parameters of the internal female reproductive organs: uterus – 4-5 month, ovaries – 5-6 and 9-10 month, uterine tubes – 5-6 and 8-9 month, vagina – 4-5 and 7-9 month. Certain nonsynchronous descending of the right and left uterine tubes into the minor pelvic cavity is found. Topographic changes of the uterine tubes are found to coincide with that of the ovaries, which is stipulated by their close syntopogenous relations.

Close interrelations between perinatal morphological transformations of the internal female reproductive organs and the processes of their histogenesis are determined. The periods of an intensive growth of hollow structures of the internal female reproductive organs are found to coincide with the periods of an intensive growth of their intra-parietal vessels and muscular layers.

At the beginning of the fetal period (4-5 month) the circular muscle fibers of the uterine tubes begin to grow to the center from the ampulla to the isthmus (diameters of these parts correlate as 1:3) with appropriate gradual increase of their diameter to the end of the 10th month of the intrauterine development. At the end of the perinatal period of human ontogenesis the circular muscle fibers of a part of the uterine tubes develop evenly. Intensive periods of ovarian growth coincide with accelerated enlargement in the size of the glandular parenchyma cells without considerable increase of their amount.

#### Conclusion.

Thus, the anatomical study conducted has solved an urgent issue of modern morphology – to determine morphological regularities of organs and structures of the female reproductive system. It forms the foundation to develop preventive, diagnostic and therapeutic methods concerning their perinatal pathology.

**Prospects of researches.** In further it is planned to investigate correlation and dynamics of morphometric parameters of internal female genital organs in adult people.

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