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CHANGES OF STRUCTURAL ORGANIZATION OF HUMAN OLFACTORY BULBS UNDER CONDITIONS OF SEVERE FORMS OF PNEUMONIA AND CEREBROVASCULAR PATHOLOGY

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Ключевые слова: *обонятельные луковицы, пневмония, цереброваскулярная патология, митральные клетки*

Abstract. Changes of structural organization of human olfactory bulbs under conditions of severe forms of pneumonia and cerebrovascular pathology. Shkodina A.D., Grinko R.M., Starchenko I.I., Vynnyk N.I., Sovhyria S.M., Kyslyi V.F. *The role of human olfactory bulbs remains one of the most interesting questions concerning work of the brain, because this organ is one in which neurogenesis is continuously generated in post-natal and adult periods. Impaired sense of smell is not a pathology that threatens human life, therefore, often remains unnoticed. However, it can directly affect the quality of life, as it leads to malnutrition and certain problems in interpersonal relationships. The study of the functional structure of the olfactory analyzer plays an important role both in clinical and experimental studies, but the question of its features in humans needs detailed research. The material of the research was 18 pairs of the olfactory bulbs of males and females aged from 30 to 90 years that were received at the Poltava Regional Department of Pathology. In order to objectify the data obtained on micropreparations, the following morphometric indices were determined: the specific gravity of the location of cellular elements; the proportion of mitral neurocytes in the entire cell population; percentage ratio of relative quantity between cellular elements, blood microvessels, fibrillar component and homogeneous eosinophilic structures. Correlation analysis of morphometric indices in the general sample revealed the existence of an inverse communication of average strength between the relative number of homogeneous eosinophilic cells and the relative number of cellular elements and blood microvessels, which in turn indicates the etiopathogenetic mechanisms of the formation of these structures. The conducted research makes it possible to conclude that mitral cells as one of the most differentiated in olfactory bulbs are sensitive to the development of hypoxic states; under the conditions of cerebrovascular pathology, the relative amount of the blood vessels of the microvessels decreases, which leads to the disorder of the trophy of the nervous tissue and as a result can lead to neurocytolysis of mitral cells. Changes in the vascular and cellular component indicate a different pathogenesis of changes in human olfactory bulbs in these pathologies and suggest that eosinophilic homogeneous cells are the result of apoptotic neurocytolysis against the background of development of hypoxic states.*

Реферат. Зміни структурної організації нюхових цибулин людини за умов тяжких форм пневмонії та цереброваскулярної патології. Шкодіна А.Д., Грінько Р.М., Старченко І.І., Винник Н.І., Совгиря С.М., Кислий В.Ф. *Роль людських нюхових цибулин у роботі головного мозку залишається одним з найцікавіших питань нейронауки, оскільки цей орган є одним з небагатьох, де нейрогенез відбувається безперервно в постанатальному та дорослому періодах. Окремо розлади нюху не розглядаються як патологія, що загрожує життю людини, тому часто залишаються непоміченими. Однак вони можуть безпосередньо впливати на якість життя, оскільки можуть призводити до проблем із харчуванням та в міжособистісних стосунках. Вивчення функціональної структури нюхового аналізатора відіграє важливу роль як у клінічних, так і в експериментальних дослідженнях, проте питання про його морфометричні особливості в людини потребує більш детального вивчення. Матеріалом дослідження були 18 пар нюхових цибулин чоловіків та жінок віком від 30 до 90 років, які було виділено на базі Полтавського обласного паталогоанотомічного бюро. З метою об'єктивізації даних, отриманих на мікропрепаратах, визначалися такі морфометричні показники: питома площа клітинних елементів; питома вага мітральних нейроцитів у всій популяції клітин; відсоткове співвідношення відносної кількості між клітинними елементами, кровоносними мікросудинами, фібрилярними компонентами та гомогенними еозинофільними тільцями. Кореляційний аналіз морфометричних показників у*

загальній сукупності вибірки виявив існування зворотного зв'язку середньої сили між відносною кількістю гомогенних еозинофільних клітин та відносною кількістю клітинних елементів та кровоносними мікросудинами, що, у свою чергу, вказує на етіопатогенетичні механізми утворення цих структур. Проведене дослідження дозволяє зробити висновок, що мітральні клітини, як одні з найбільш диференційованих у нюхових цибулинах, чутливі до розвитку гіпоксичних станів. Таким чином за умов цереброваскулярної патології відносна кількість кровоносних мікросудин зменшується, що призводить до порушення трофіки нервової тканини і, як наслідок, може призвести до нейроцитолізу мітральних клітин. Зміни судинного та клітинного компонентів вказують на різний патогенез змін нюхових цибулин при цих патологіях і свідчать про те, що еозинофільні гомогенні клітини є результатом апоптотичного нейроцитолізу на тлі розвитку гіпоксичних станів.

From an evolutionary point of view the sense of smell is one of the most ancient and most essential sensations through which the process of knowledge of the external world takes place. For most species of mammalian the analysis of odorants determines the complex forms of behavior on which their life depends [4]. Unlike other analyzers, chemosensory systems are dynamic throughout the period of ontogenesis due the processes of continuous renewal of olfactory epithelium. Through the reticular formation, the olfactory system is closely linked to the autonomic nervous system, which explains reflex responses of the digestive and respiratory systems. Separate studies show varying sensitivity to certain odorants in men and women while significant gender differences in the structure of the leading part of the olfactory analyzer have not been identified, which suggests the expediency of further in-depth studies of the peculiarities of the structural organization of olfactory bulbs (OB) and olfactory epithelium [17]. At the same time the age factor significantly affects the olfactory perception, which is associated with changes in the hormonal status of the human body in the process of ontogenesis [2].

Olfactory dysfunction is a fairly widespread symptom of many neurodegenerative diseases, which is probably arise due to lesions of mediator systems at different levels of the analyzer [7]. Separately impaired sense of smell is definitely not a pathology that threatens human life, therefore, often remains unnoticed. However, they can directly affect the quality of life, as it leads to malnutrition and certain problems in interpersonal relationships [14]. There are studies that confirm the changes in the volume of OB and as a consequence of olfactory dysfunction in patients with psychotic and neurological disorders. Thus under normal conditions of the aging process, the total number of neurons in OB does not decrease, but under the condition of Alzheimer's disease in these structures there is a process of loss of nerve cells [5]. The first stage of the development of non-motor disorders in Parkinson's disease is characterized by degeneration of the olfactory bulb and the anterior olfactory nucleus, which can clinically be manifested as an impaired sense of smell [1, 3, 6].

The study of the functional structure of the olfactory analyzer plays an important role both in clinical and experimental studies, but the question of its features in humans needs detailed research. The role of human OB remains one of the most interesting questions concerning the work of brain, since this organ is one of the few whose interneurons are continuously generated in post-natal and adult life. Their main functions are the threshold of perception, discrimination and identification of smells [13].

The aim of research was to investigate morphofunctional features of human olfactory bulbs in patients with severe forms of pneumonia and cerebrovascular pathology.

MATERIALS AND METHODS OF RESEARCH

The material of the research was 18 pairs of the OB of males and females aged from 30 to 90 years that were received at the Poltava region Department of Pathology. The samples were divided into 3 groups according to the causes of death in accordance with the pathoanatomical conclusion:

- group 1 (first experimental group) – OB of people who died of severe forms of pneumonia (n=5);
- group 2 (second experimental group) – OB of people who died of cerebrovascular pathology (n=7);
- group 3 (control group) – OB of people whose cause of death was not associated with the specified pathological conditions (n=6).

After fixation in 10% neutral formalin, the material was dehydrated and paraffin waxed according to a conventional method. From the paraffin blocks on the rotational microtome, histological sections were made, which were stained with H&eosin [16], picrofuxin by Van Gieson [8], and methylene blue by Nissl [12]. To investigate micropreparations and to conduct morphometric studies, optical microscope BX-41 of the company «Olympus» with a set of corresponding licensing programs was used.

In order to objectify the data obtained on micropreparations, the following morphometric indices were determined [9]:

- the specific gravity of the location of cellular elements (at 50000 μm^2);

- the proportion of mitral neurocytes in the entire cell population;

- percentage ratio of relative quantity between cellular elements, circulatory microcosms, fibrillar component and homogeneous eosinophilic structures.

The obtained data were subjected to statistical processing. Medians (Me) and its interquartile interval (Q1-Q3) were calculated for each variation line. We applied the criteria of Shapiro-Wilk and Kolmogorov-Smirnov in order to evaluate the normality of distribution. Since the distribution differed from normal, nonparametric methods were used for statistical analysis – U-test of Mann-Whitney (for two independent groups) and Spearmen linear correlation coefficient. Statistical calculations were performed using the free statistical software EZR 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria) [10]. The results were considered statistically significant at $p \leq 0.05$.

RESULTS AND DISCUSSION

Materials investigation with the help of small magnifications of a light microscope indicates that OB are a set of heterogeneous morphological features of nerve cells, glial cell elements, blood microvessels and fibrillar structures, which are surrounded by a peculiar capsule that is filled with pia mater and partially subarachnoid one. The dura mater in this zone forms a tent of olfactory bulbs. Immediately in the capsule, a significant amount of collagen fibers, cells of the fibroblast type, deposits of melanin and blood vessels are determined. In healthy people its volume is 65-70 mm^3 that correlates with the functional activity of the olfactory system. In the internal space of OB, five layers are distinguished, differing in their morphological characteristics and, accordingly, in the functions they perform: glomerular, external pleximorphic, a layer of mitral cells, granular, internal pleximorphic (Fig. 1).

Specific gravity of the location of cellular elements in the internal structure of the olfactory bulb varies from 32 to 158 per 50.000 μm^2. According to a study conducted, in OB of the first group this feature was 105.5 (76.85-142.35), in the second – 104.5 (86.75-133.45) and the third – 105.0 (84.35-137.95), being not significantly different.

Mitral neurocytes are phylogenetically the oldest and largest cells of the OB. Their total number is relatively small and amounts to approximately 5% of the entire cellular population of olfactory bulbs. A characteristic feature of mitral cells is the presence of a dendritic protoplasmic barrel, which passes to the glomerular zone that forms a dense branch, and the axons pass along with the axons adjacent to the periglomerular cells in the limbic system (Fig. 2).

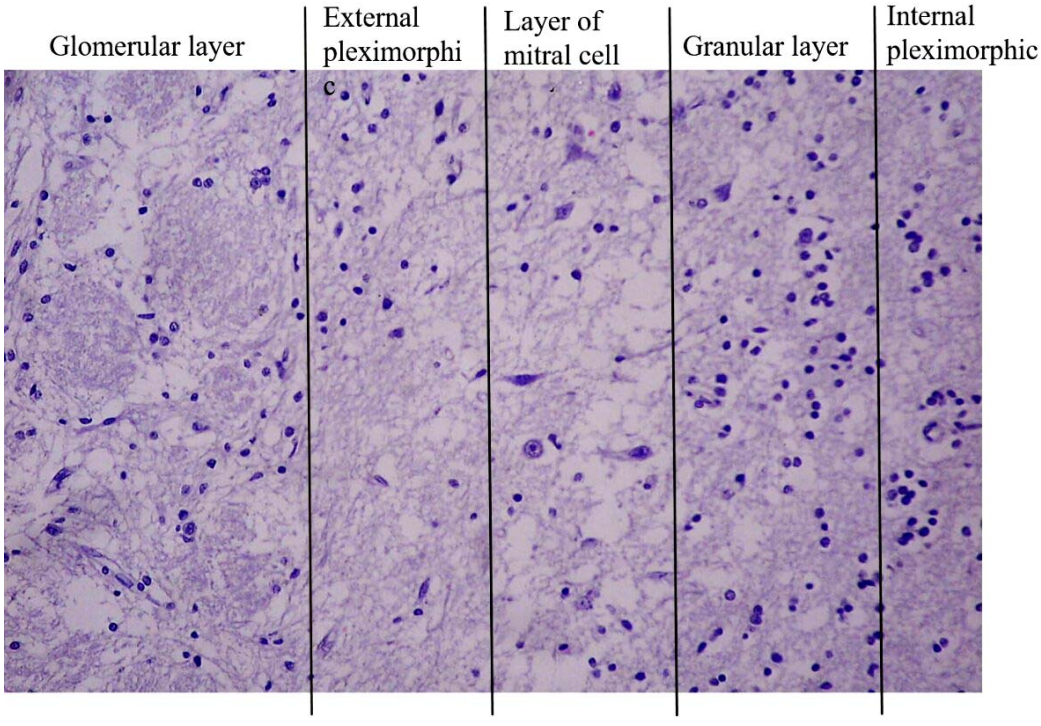

Fig. 1. Internal structure of human olfactory bulbs (H&eosin stain, magnification 400x)

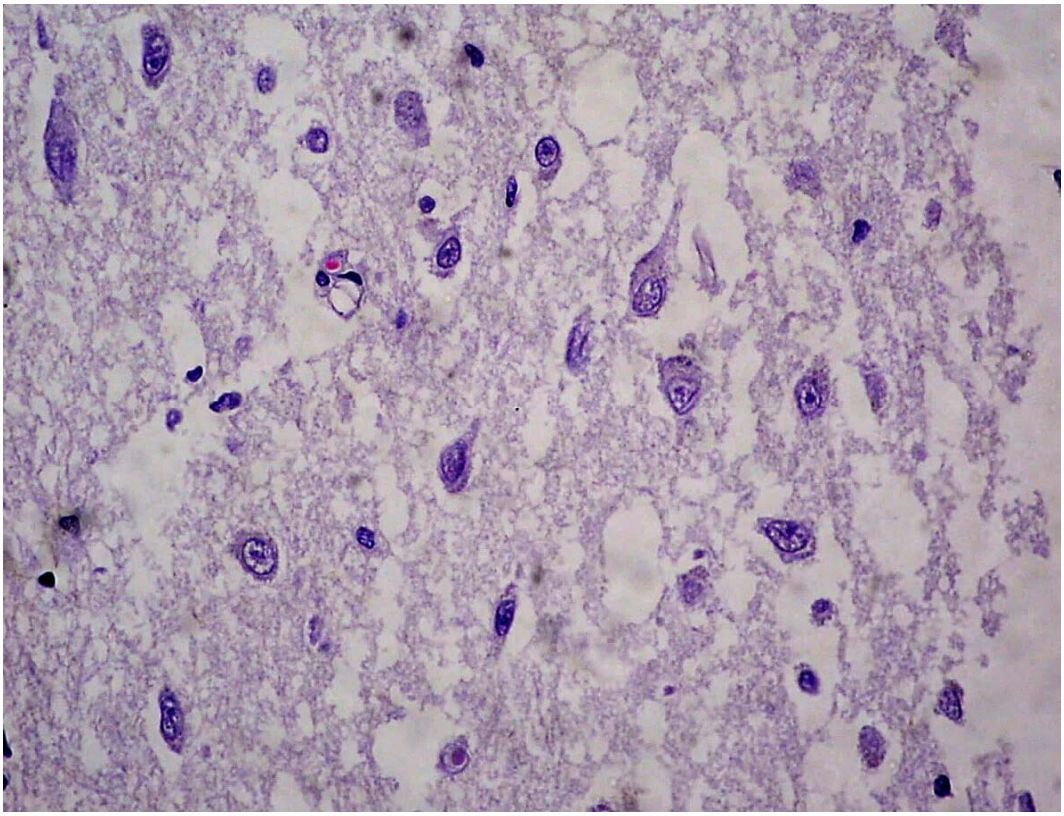

Fig. 2. Layer of mitral cells of olfactory bulbs (H&eosin stain, magnification 400x)

It was found that the proportion of these cells in the group 1 – 1.75 (1.5-2.05), in the group 2 – 4.05 (1.95-4.65), in the group 3 –5.68 (4.75-6.25). Thus, a significant decrease in the proportion of mitral neurocytes in the total cell population was found in samples from people who suffered from severe forms of pneumonia (Fig. 3).

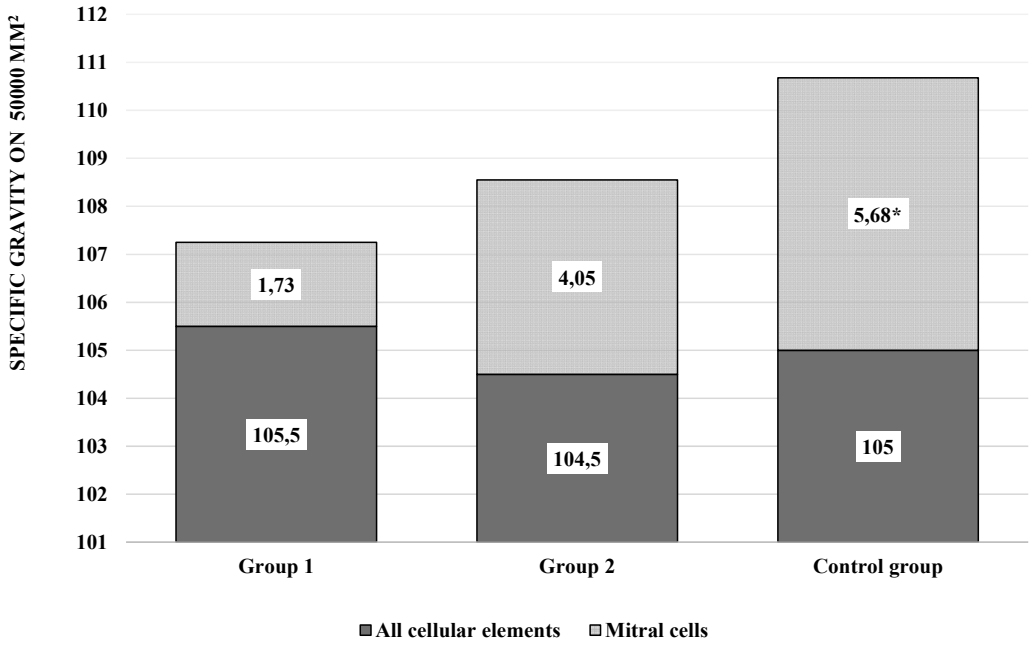

Fig. 3. Specific gravity of cellular elements in human OB (* – p≤0.05 relative to group 1)

The blood supply to the OB is provided by the microvessels both of arterial and venous types which occupy 1-2% of the internal space. Not only the vessels of the Willis circle, but also their small branchlets, are affected under the conditions of development of cerebrovascular pathology.

The part of internal structure occupied by microvessels in the group 1 was 1.05 (0.98-1.17), in the group 2 – 1.42 (1.12-1.65) in comparison to control group in which this feature was 1.58 (1.24-1.72). This research shows that statistically significant changes on control in the group of severe forms of pneumonia were not detected, while the percentage of blood vessels in the internal space of OB in the group 1 decreased relative to the control group.

Generally, the fibrillar components of the 1st group occupied 92.34 (89.65-96.32), in the 2nd group – 93.56 (91.02-97.35) and in the 3rd group 93.15 (89.24-96.42) in the internal space of OB. There was no statistically significant difference between these figures.

There were significant changes relative to the number of mitral neurons in OB of those who died of severe forms of pneumonia compared to those in whom the specified pathology did not decrease by 23.02%. Patients suffering from vascular pathology revealed a decrease in the relative number of mitral neurons by 64%.

In addition to the above-described elements in the composition of OB it should be noted the presence of rounded, larger homogeneous eosinophilic bodies which are similar to described ones in other parts of the brain “shadow cells” (Fig. 4).

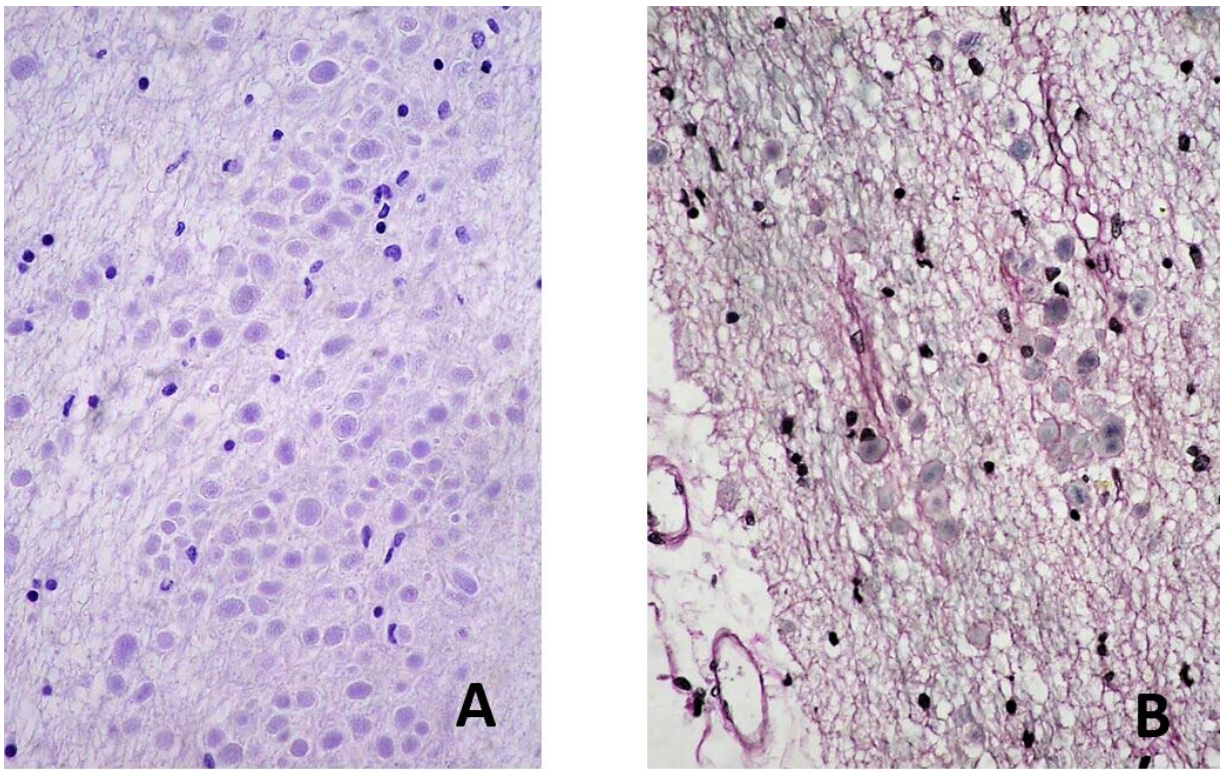

Fig. 4. “Shadow cells” in a human olfactory bulb
(A – H&eosin stain, B – Van Gison stain, magnification 400x)

In the cerebral hemispheres and cerebellum, these structures are described as mummified nerve cells due to incomplete neurocytolysis, which occurs in response to hypoxic lesions. The evaluation of morphometric indices found that in the group 1 their specific gravity was 2.3 (1.98-2.67), in the group 2 – 1.16 (0.98-1.26) and in control group – 0.18 (0.15-0.35).

The study defines that under the condition of cerebrovascular pathology the relative number of homogeneous eosinophilic entities significantly increased by 53% compared with group 3, and in severe forms of pneumonia by 50.79% compared with group 2 and almost by 12 times compared with the control group. In the amount of up to 0.5% “shadow cells” can be detected in samples of the deceased from causes not associated with the pathological conditions under study. There was no association between the presence of investigated structures, age and sex, which indicates their pathological origin (Table).

Percentage ratio of the relative number of elements of the internal structure of the OB, Me (Q1-Q3)

Feature	Group 1 (n=5)	Group 2(n=7)	Control group (n=6)
Cellular elements	4.27 (3.54-4.81)	3.62 (2.12-3.77)*	4.85 (3.95-5.23)
Microvessels	1.05 (0.98-1.17)*	1.42 (1.12-1.65)	1.58 (1.24-1.72)
Fibrillar components	92.34 (89.65-96.32)	93.56 (91.02-97.35)	93.15 (89.24-96.42)
"Shadow cells"	2.3 (1.98-2.67)**/*	1.16 (0.98-1.26)*	0.18 (0.15-0.35)

Notes. * – p≤0,05 relative to control group, ** – p≤0,05 relative to group 2.

Correlation analysis of morphometric indices in the general sample population revealed the existence of an inverse communication of average strength between the relative number of homogeneous eosinophilic cells and the relative number of cellular elements (r= -0.67; p=0.017) and blood microvessels (r= -0.54; p=0.034), which in turn indicates the etiopathogenetic mechanisms of the formation of these structures.

Changes in blood supply were found in the olfactory bulbs of people suffering from cerebrovascular pathology. Their significant reduction may indicate a decreasing of vascularization and, as a consequence, organ trophism.

The specific location of cellular elements is not changed with the development of pneumonia and cerebrovascular diseases. As known, some type of pneumonia may modulate mRNA expression level of neurotrophic factor and its effects on the activation and viability of microglia [15]. In persons suffering from severe forms of pneumonia, there was a decrease in the proportion of the other neurons of the olfactory analyzer – mitral cells, which can lead to disorders of olfactory perception. It can occur due to hypoxic neurotrophic disturbances. However, their number decreases in both types of studied pathological conditions.

In the case of severe pneumonia, such changes may be due to oxygen-dependent processes in the nerve cell itself, while in cerebrovascular disease the main cause may be trophic disorders due to reduced vascularization.

The appearance of "shadow cells", which are described in other brain structures as markers of hypoxia and apoptosis [11], and their association with the quantitative composition of cellular components and the specific area of microvessels indicates the development of neurocytolysis of mitral cells with different genesis.

CONCLUSIONS

The work describes the internal structure of human olfactory bulbs and identifies 5 structural layers that differ in morphological structure. The analysis showed that under conditions of cerebrovascular pathology, the comparative number of blood vessels decreases, that leads to disruption of trophic nerve tissue, and can lead to neurocytolysis of mitral cells. The research of changes in the internal structure of human olfactory bulbs has shown that the development of severe forms of pneumonia is accompanied by changes in cellular composition and decrease the number of mitral cells. The analysis of the structural changes of human olfactory bulbs indicates the different genesis of their development and suggests that eosinophilic homogeneous bodies are the consequence of apoptotic neurocytolysis against the background of hypoxic conditions.

Conflict of interests. The authors declare no conflict of interest.

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