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FEATURES OF THE EARLY MORPHOGENESIS OF THE CENTRAL NERVOUS SYSTEM

T. Khmara, O. Tsyhykalo, I. Zamorskii, T. Pankiv, T. Komshuk, O. Smetaniuk

Bukovinian State Medical University
(Chernivtsi, Ukraine)

Summary

One of the urgent tasks of modern medicine is the prevention of brain damage during the human fetal period and the creation of conditions that ensure proper brain development.

Objective of the research. *To find out the features of the early morphogenesis of the central nervous system in the embryonic and early pre-fetal periods of human ontogenesis.*

Methods. *The study of the early stages of the formation of the brain and spinal cord was carried out on 14 embryos and 12 human fetuses with 4.5-20.0 mm parietal-caudal length (PCL) by the methods of microscopy, three-dimensional computer reconstruction, morphometry, and statistical processing of digital data.*

The investigations were performed keeping to the major regulations of the Resolution of the First National Congress on Bioethics «General Ethic Principles of Experiments on Animals» (2001), ICH GCP (1996), the European Union Convention on Human Rights and Biomedicine (04.04.1997), and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (18.03.1986), the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (1964-2008), EU Directives № 609 (24.11.1986), the Orders of the Ministry of Health of Ukraine № 690 dated 23.09.2009, № 944 dated 14.12.2009, № 616 dated 03.08.2012.

The work is carried out within the framework of the initiative research work of the Department of Histology, Cytology and Embryology of Institution of the Bukovinian State Medical University «Structural and functional peculiarities of tissues and organs in ontogenesis, regularities of variant, constitutional, sex-, age-related and comparative human morphology». State registration number: 0121U110121. Terms of execution: 01.2021-12.2025.

Results. *There is a close relationship between the development of the cerebral cavity, in particular, its ventricles, and the morphogenesis of the corresponding parts of the brain. In the process of complications in the structure of the ventricles of the brain, namely during the formation of the vascular plexus, disturbances can occur, which cause defects in the subsequent stages of ontogenesis. On the basis of the above, this period (the 6th week of embryonic development) can be classified as critical.*

Conclusion. *In embryos of 6.0-8.0 mm PCL, the formation of primitive, without the formation of corresponding parts, lateral ventricles and the third ventricle of approximately elliptical shape is determined. In embryos of 9.0-12.0 mm PCL, the contours of the medulla oblongata are defined, which is a continuation of the spinal cord, the central channel of which forms the cavity of the fourth ventricle in the shape of a diamond. At the end of the embryonic period (embryos 12.0-13.5 mm PCL), accelerated development of the terminal and hindbrain is observed, which leads to a change in the configuration of the brain cavity, in which the anterior and lower horns of the lateral ventricles can be distinguished. At 16.0-18.0 mm PCL of human fetuses, the formation of the cerebral vascular plexus begins, which is represented by insignificant folds with barely noticeable protrusions on the ependymal membrane of the brain cavity.*

Key words: *Central Nervous System; Brain; Spinal Cord; Development; Embryo; Fetus; Human.*

Introduction

It is known that the quality of future life depends on the correct formation of organs and systems. The processes of the birth of a new life and the peculiarities of the development of the embryo and fetus have always attracted the attention of anatomists, since it is obvious that in this prenatal period, which is hidden from the eyes, very important processes of morphogenesis of tissues and organs take place [1]. Difficulties in studying the characteristics of embryo and fetogenesis – the intimate aspects of the birth of a new life and the taboo of using the human being as an «experimental» model have hindered the acquisition of comprehensive information about the prenatal ontogenesis of a person [2]. As a result, there are a number of gaps in human embryology and fetal anatomy that have been attempted to be filled by research on laboratory animals [3-5].

Without a detailed study of the correct development of the fetus, without knowledge of neurogenesis, conditions and causes of intrauterine developmental disorders, prevention and correction of birth defects is impossible [6-8]. The study of the characteristics of the sources and the chronological sequence of the formation of the central nervous system, which regulates the development of the child's body in normal conditions, is especially valuable and necessary for the understanding of all complex physiological processes in the body. The life and health of a person from the moment of his birth are connected with the external, constantly changing environment and with those physiological reactions of the internal environment, which are considered normal during the correct prenatal development of a person. The problem of the influence of harmful factors on the development of the brain and spinal cord cannot be solved without simultaneously studying the principles and patterns of brain development [9]. One of the urgent tasks of modern medicine is the prevention of brain damage during the fetal period of a person and the creation of conditions that ensure proper brain development [10, 11]. At the same time, the conscious management of the process of brain development requires the study of the main stages of transformation of the external form and internal structure of the brain. From the point of view of chemical composition and structure, the brain is the most complex organic formation [12, 13]. Each stage of prenatal human neuroontogenesis is characterized by its own specific structural and functional features of brain and spinal cord development [14].

The purpose of the study. To find out the features of the early morphogenesis of the central nervous system in the embryonic and early pre-fetal periods of human ontogenesis.

Material and methods

The study of the early stages of the formation of the brain and spinal cord was carried out on 14 embryos and 12 human pre-fetuses of 4.5-20.0 mm parietal-coccigeal length (PCL) by the methods of microscopy, three-dimensional computer reconstruction, morphometry, and statistical processing of digital data.

The investigations were performed keeping to the major regulations of the Resolution of the First National Congress on Bioethics «General Ethic Principles of Experiments on Animals» (2001), ICH GCP (1996), the European Union Convention on Human Rights and Biomedicine (04.04.1997), and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (18.03.1986), the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (1964-2008), EU Directives № 609 (24.11.1986), the Orders of the Ministry of Health of Ukraine № 690 dated 23.09.2009, № 944 dated 14.12.2009, № 616 dated 03.08.2012.

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Research results and their discussion

In the 3rd week of intrauterine development, the source of the nervous system takes place, which initially has the appearance of a plate located on the dorsal side of the embryo. As a result of the growth of the edges of the neural plate, a groove is formed, then its edges close, and the groove turns into a neural tube. Later, at the anterior end of the neural tube, bulges with cavities appear one after another – vesicles of the brain. It is known that in the later stages of intrauterine development the anterior and posterior cerebral vesicles divide into two each, and five cerebral vesicles are formed. The spinal cord is formed from the part of the neural tube located behind the fifth medulla. (Fig. 1).

Figure. 1. Sagittal section of a human embryo 4.5 mm PCL (hematoxylin and eosin). Photo of the microspecimen. Magn. x80:

1 – intermediate brain; 2 – midbrain; 3 – hindbrain; 4 – spinal cord; 5 – terminal brain (neuroectoderm of the otic placode); 6 – heart; 7 – mandibular process of the first pharingeal arch; 8 – maxillary process of the first pharingeal arch; 9 – rudiment of the spinal column.

It should be noted that in embryos of 4,5-5,0 mm CPL the walls of the cavities of the brain vesicles consist of two layers: the inner – ependymal layer and the outer – an insignificant layer of connective tissue. Lateral ventricles, as anatomical formations of the terminal brain, are not detected at this stage of embryonic development. In embryos of 6.0-7.0 mm CPL, telencephalic vesicles are formed from the lateral projections of the anterior brain vesicle, from which the hemispheres of the terminal brain will develop in the future (**Fig. 2**). The cavities of the telencephalic vesicles are approximately crescent-shaped. In the middle sections, they are widely connected both with each other and with the dorsal part of the cavity of the anterior vesicle of the brain, which later becomes the third ventricle. Note that this stage of embryogenesis begins with the gradual transformation of this extremely simple structure into a complex system that is the lateral ventricle.

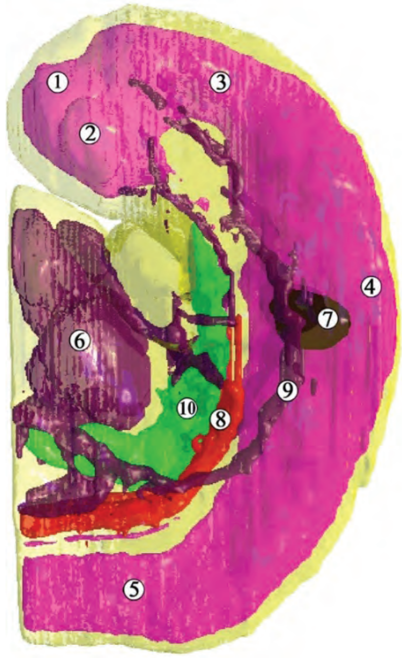

Figure 2. **Three-dimensional computer reconstruction of the cranial half of the human embryo 4.5 mm PCL. Left lateral projection. Magn. x80.**

1 – intermediate brain; 2 – terminal brain; 3 – middle brain; 4 – posterior brain; 5 – spinal cord; 6 – heart; 7 – otic placode; 8 – dorsal arta; 9 – posterior cardinal vein; 10 – the cavity of the foregut.

In embryos of 6.0-8.0 mm PCL, due to the formation of the orbit, the terminal and intermediate medulla are demarcated, the development of the third ventricle begins, and the formation of interventricular openings connecting the third and lateral ventricles is observed. As a result of thickening of the lateral walls of the diencephalon, the cavity of the third ventricle acquires a goblet shape. This thickening is the beginning of the formation of the thalamus. In embryos of 6.0-8.0 mm PCL, due to the formation of the orbit, the terminal and intermediate medulla are demarcated, the development of the third ventricle begins, and the formation of interventricular openings connecting the third and lateral ventricles is observed. As a result of thickening of the lateral walls of the diencephalon, the cavity of the third ventricle acquires a goblet shape. This thickening is the beginning of the formation of the thalamus.

In embryos of 9.0-10.0 mm PCL, the third ventricle has an elliptical shape, its longitudinal size is 1.4±0.1 mm, transverse – 0.2±0.06 mm.

In embryos of 9.0-12.0 mm PCL the contours of the medulla oblongata, which is a continuation of the spinal cord, are determined (Fig. 3). At the same time, the central canal of the spinal cord forms the cavity of the fourth ventricle, which has the shape of a rhombus. The dorsal wall of the hindbrain is thin and consists of a single layer of ependymal cells. The lateral parts of the hindbrain thicken and give rise to the cerebellar plate. The ventral parts of the hindbrain grow to form the pons and middle cerebellar peduncles.

Figure. 3. **Sagittal section of embryo 10.0 mm PCL (hematoxylin and eosin). Photo of the microspecimen. Magn.x80:**

1 – medulla oblongata; 2 – rudiment of the spinal cord; 3 – cavity of the fourth ventricle; 4 – rudiment of the choroid, 5 – rudiment of the dura mater.

In embryos with 11.0-13.0 mm PCL, the cavity of the third ventricle narrows and gradually acquires a diamond shape. The longitudinal size of the third ventricle is 1.8±0.4 mm and the transverse size is 0.3±0.05 mm. Interventricular foramina decrease in diameter. The length of the plate of the roof of the diencephalon is 3.4±0.5 mm, its width in the anterior part is 0.5±0.1 mm and in the posterior part – 0.2±0.01 mm, the thickness of the plate reaches 6.0±1.5 mm. During this period the vascular plexus of the third ventricle is formed.

There is a close relationship between the development of the cerebral cavity, especially its ventricles, and the morphogenesis of the corresponding parts of the brain. In the process of complication of the structure of the ventricles of the brain, namely, during the formation of the vascular plexus, disturbances can occur, which cause the appearance of defects in the subsequent stages of ontogenesis. On the basis of the above, this period (the 6th week of embryonic development) can be classified as critical.

At the end of the embryonic period, accelerated development of the terminal and hindbrain is noted, which leads to rapid differentiation of parts of the brain and their cavities, and slowed growth of the midbrain. The formation of the lateral ventricles occurs under the direct influence of the development of the hemispheres themselves and the differentiation of their internal structures.

In fetuses of 11.5-15.0 mm PCL, a protrusion appears on the ventral wall of the lateral ventricle, represented by the rudiment of the striatum. An important component of the lateral ventricles is the vascular plexus, which appears as an intussusception of the medial ventricular wall in the form of a barely noticeable fold (Figs. 4, 5). In fetuses with a PCL of 18.0-20.0 mm, this fold is located dorsal to the level of the interventricular septum and is attached to the medial wall of the lateral ventricle along its entire length. At the periphery of the plexus, single fold projections are observed, which are the beginning of the further branched structure of the plexus.

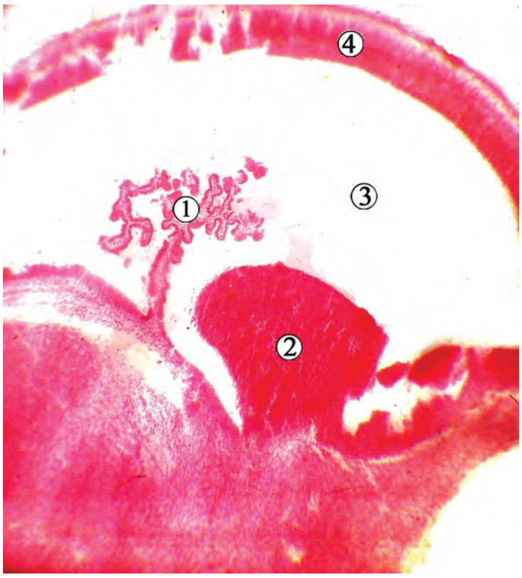

Figure 4. Sagittal section of an embryo of 11.5 mm PCL (hematoxylin and eosin). Photo of the microspecimen. Magn. x80:

1 – vascular plexus of the lateral ventricle; 2 – rudiment of the striatum; 3 – right lateral ventricle; 4 – the rudiment of the cerebral plate of the hemispheres of the terminal brain.

In fetuses with a PCL of 16.0-18.0 mm, a vascular plexus begins in the area of the dorsal wall of the fourth ventricle in the form of a strip running along the upper wall and facing the ventricular cavity. The length of the stripe reaches 1.8 mm, the width is 40.0-42.0 μm. The plexus is a series of closely spaced tubercles with a height of 34.0-38.0 μm. In the examined fetuses the cerebellum is represented only by a thin plate, which closes behind the cavity of the fourth ventricle in its rostral part.

In fetuses with a PCL of 17.0-19.0 mm, the forebrain approaches the ventral surface of the rhomboid brain due to the curvature of the brain tube. The third ventricle has a rhomboid shape, its length is 3.0±0.5 mm and its width is 0.5±0.04 mm. In the central part of the diencephalic roof, behind the choroid plexus, the source of the pineal gland appears in the form of a small prominence in which a small cavity is defined. In the course of development, the pineal gland gradually shifts dorsally and only at the beginning of the pre-fetal period becomes a component of the posterior wall of the third ventricle.

The smallest changes in this period of development in comparison with other cerebral vesicles occur in the midbrain. It should be noted that the cavity of the midbrain gradually narrows due to the thickening of its ventral and lateral walls, and in pre-fetuses 19.0-20.0 mm PCL turns into the cerebral aqueduct connecting the cavity of the third ventricle with the cavity of the fourth ventricle. The cerebellum develops from the thickenings of the dorsolateral edges of the rhomboid brain at the point where they converge and enter the isthmus separating the rhomboid brain from the midbrain. Between these thickenings is a thin roof plate that forms the upper wall of the fourth ventricle.

Our research on the early formation of primitive lateral and third ventricles correlates with modern understanding of central nervous system development. Studies emphasize that at this time the telencephalon forms and the lateral ventricles appear as hollow spaces that are still largely undifferentiated [15-17]. This primitive state is a foundational stage for later complex brain structures.

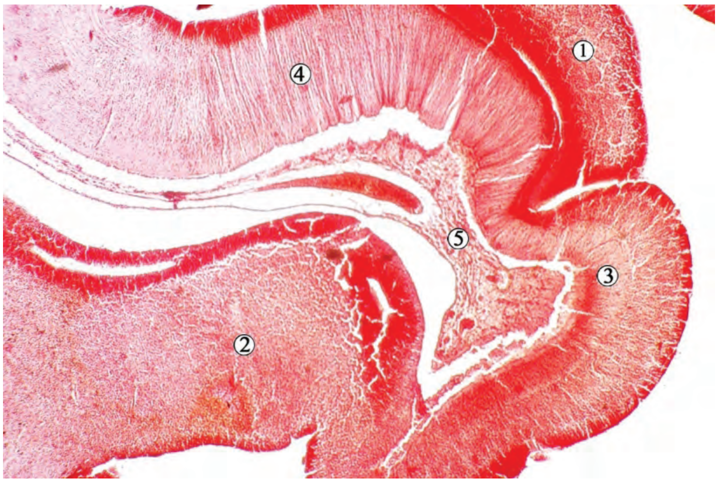

Figure. 5. Sagittal section of the pre-fetus 15.0 mm PCL (hematoxylin and eosin). Photo of the microspecimen. Magn. x80:

1 – striated body; 2 – cerebral ventral plate of the terminal brain; 3 – cerebral lateral plate of the diencephalon; 4 – cerebral ventral plate of the rhomboid brain; 5 – vascular membrane of the brain.

The development of the medulla oblongata and the formation of the fourth ventricle, described as a rhomboid shape, mirrors descriptions of how the neural tube expands to form specific brain regions, such as the hindbrain [18]. At this stage, the medulla begins to clearly differentiate from the spinal cord, and the central canal forms the primitive fourth ventricle [19-20].

The accelerated growth of the forebrain and hindbrain, leading to structural changes in the ventricular cavities, is well documented in neuroembryology. Research suggests that the lateral ventricles begin to form horns (anterior and inferior) as the forebrain expands, consistent with our observation [21-23].

Our data on the initiation of choroid plexus formation are consistent with studies showing that during this stage, small folds and protrusions in the ependymal lining begin to produce cerebrospinal fluid [24]. The early formation of the choroid plexus is critical for regulating the fluid environment of the brain [25-27].

Overall, our results are consistent with current research showing a clear progression from primitive ventricular formation to the development of the choroid plexus, which is critical for central nervous system structure and function.

Conclusions

1. In embryos of 6.0-8.0 mm PCL, the development of primitive, without the formation of corresponding parts, lateral ventricles, and the third ventricle of an approximate elliptical shape is determined.

2. In embryos of 9.0-12.0 mm PCL, the contours of the medulla oblongata are determined, which is a continuation of the spinal cord, the central channel of which forms the cavity of the fourth ventricle in the shape of a diamond.

3. At the end of the embryonic period (embryos 12.0-13.5 mm PCL), accelerated development of the terminal and hindbrain is observed, which leads to a change in the configuration of the brain cavity, in which the anterior and lower horns of the lateral ventricles can be distinguished.

4. In human pre-fetuses of 16.0-18.0 mm PCL, the formation of the vascular plexus of the brain begins, which is represented by minor folds with barely noticeable protrusions on the ependymal membrane of the brain cavity.

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ОСОБЛИВОСТІ РАННЬОГО МОРФОГЕНЕЗУ ЦЕНТРАЛЬНОЇ НЕРВОВОЇ СИСТЕМИ

Т. В. Хмара, О. В. Цигикало, І. І. Заморський, Т. В. Паньків, Т. С. Комшук, О. В. Сметанюк

Буковинський державний медичний університет
(м. Чернівці, Україна)

Резюме.

Одним із актуальних завдань сучасної медицини є запобігання ушкодженням мозку під час внутрішньоутробного періоду людини та створення умов, що забезпечують правильний розвиток мозку.

Мета дослідження. З'ясувати особливості раннього морфогенезу центральної нервової системи в зародковому та на початку передплодового періодів онтогенезу людини.

Матеріал і методи дослідження. Дослідження ранніх етапів формування головного та спинного мозку проведено на 14 зародках та 12 передплодах людини 4,5-20,0 мм тім'яно-куприкової довжини (ТКД) методами мікроскопії, тривимірного комп'ютерного реконструювання, морфометрії та статистичної обробки цифрових даних. Дослідження проводилося відповідно до основних положень Резолюції Першого національного конгресу з біоетики «Загальні етичні принципи експериментів на тваринах» (2001), ICH GCP (1996), Конвенції Європейського Союзу про права людини та біомедицину (1997), а також Гельсінської декларації про етичні принципи медичних досліджень із залученням людей (1964-2008), Директив ЄС № 609 (1986), Наказів МОЗ України № 690 від 23.09.2009, № 944 від 14.12.2009, № 616 від 03.08.2012. Робота виконується в рамках ініціативної науково-дослідної роботи кафедри гістології, цитології та ембріології Буковинського державного медичного університету «Структурно-функціональні особливості тканин і органів в онтогенезі, закономірності варіантної, конституційної, статево-вікової та порівняльної морфології людини». Державний реєстраційний номер: 0121U110121. Терміни виконання: 01.2021-12.2025.

Результати. Спостерігається тісний взаємозв'язок між розвитком порожнини головного мозку, зокрема його шлуночків, та морфогенезом відповідних частин мозку. В процесі ускладнення будови шлуночків головного мозку, а саме в період утворення судинного сплетення, можуть відбуватися порушення, які спричиняють виникнення вад на подальших етапах онтогенезу. На підставі вище зазначеного цей період (6-й тиждень ембріонального розвитку) можна віднести до критичних.

Висновки. У зародків 6,0-8,0 мм ТКД визначається формування примітивних, без утворення відповідних частин, бічних шлуночків та третього шлуночка наближеної еліпсоподібної форми. У зародків 9,0-12,0 мм ТКД визначаються контури довгастого мозку, що є продовженням спинного мозку, центральний канал якого утворює порожнину четвертого шлуночка у формі ромба. Наприкінці зародкового періоду (зародки 12,0-13,5 мм ТКД) спостерігається прискорений розвиток кінцевого та заднього мозку, що призводить до зміни конфігурації порожнини головного мозку, в якій можна виділити передній та нижній роги бічних шлуночків. У передплодів людини 16,0-18,0 мм ТКД започатковується формування судинного сплетення головного мозку, яке представлене незначними складками з ледь помітними випинами на епендимній оболонці мозкової порожнини.

Ключові слова: центральна нервова система; головний мозок; спинний мозок; розвиток; зародок; передплід; людина.

Contact information:
Tatiana Khmara – MD, professor, professor of the Department of Human Anatomy named after MG Turkevich of the Bukovinian State Medical University, Chernivtsi, Ukraine.
e-mail: khmara.tv.6@gmail.com
ORCID ID: https://orcid.org/0000-0003-4699-6600
Researcher ID: C-9964-2017
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=57209663496

Olexandr Tsyhykalo – MD, professor, head of the Department of Histology, Cytology and Embryology of Bukovinian State Medical University, Chernivtsi, Ukraine.
e-mail: tsyhykalo.olexandr@bsmu.edu.ua
ORCID ID: https://orcid.org/0000-0003-2302-426X
Researcher ID: C-3676-2017
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=57195933570

Ihor Zamorskii – MD, professor, head of the Department of Pharmacology of the Bukovinian State Medical University, Chernivtsi, Ukraine.
e-mail: igor.zamorskii@gmail.com
ORCID ID: https://orcid.org/ 0000-0003-0947-6729
Researcher ID: N-7652-2016
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=6507286431

Tetiana Pankiv – phD, assistant of the Department of Pathological Anatomy of the Bukovinian State Medical University, Chernivtsi, Ukraine.
e-mail: komar.tetiana.ls14@bsmu.edu.ua
ORCID ID: https://orcid.org/ 0000-0003-0947-6729
Researcher ID: https://researchid.com/komartetiana
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=581007892006507286431

Tetiana Komshuk – Doctor of Biological Sciences, director of Kivertsivskyi of the professional medical college of the Volyn regional council, Kivertsi, Ukraine.
e-mail: medcolledge.kiv@gmail.com
ORCID ID: https://orcid.org/0009-0006-5753-4873

Oleksii Smetaniuk – PhD, Assistant Professor, Department of Medical Biology and Genetics, Bukovinian State Medical University (Chernivtsi, Ukraine).
e-mail: smataniuk.oleksii@bsmu.edu.ua
ORCID ID: https://orcid.org/orcid-search/search?searchQuery=0000-0002-8985-2650
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=57448533900

Контактна інформація:
Хмара Тетяна Володимирівна – д.мед.н., професор, професорка кафедри анатомії людини ім. М. Г. Туркевича закладу вищої освіти Буковинського державного медичного університету (м. Чернівці, Україна).
e-mail: khmara.tv.6@gmail.com
ORCID ID: https://orcid.org/0000-0003-4699-6600
Researcher ID: C-9964-2017
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=57209663496

Цигикало Олександр Віталійович – д.мед.н., професор, завідувач кафедри гістології, цитології та ембріології Буковинського державного медичного університету (м. Чернівці, Україна).
e-mail: tsyhykalo.olexandr@bsmu.edu.ua
ORCID ID: https://orcid.org/0000-0003-2302-426X
Researcher ID: C-3676-2017
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=57195933570

Заморський Ігор Іванович – д.мед.н., професор, завідувач кафедри фармакології Буковинського державного медичного університету (м. Чернівці, Україна).
e-mail: igor.zamorskii@gmail.com
ORCID ID: https://orcid.org/ 0000-0003-0947-6729
Researcher ID: N-7652-2016
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=6507286431

Паньків Тетяна Василівна – доктор філософії, асистентка кафедри патологічної анатомії Буковинського державного медичного університету (м. Чернівці, Україна.
e-mail: komar.tetiana.ls14@bsmu.edu.ua
ORCID ID: https://orcid.org/ 0000-0003-0947-6729
Researcher ID: https://researchid.com/komartetiana
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=581007892006507286431

Комшук Тетяна Сергіївна – д. біол. наук, директорка Ківерцівського фахового медичного коледжу Волинської обласної ради (м. Ківерці, Україна).
e-mail: medcolledge.kiv@gmail.com
ORCID ID: https://orcid.org 0009-0006-5753-4873

Сметанюк Олексій Васильович – доктор філософії, асистент кафедри медичної біології та генетики Буковинського державного медичного університету (Чернівці, Україна)
e-mail: smataniuk.oleksii@bsmu.edu.ua
ORCID ID: https://orcid.org/orcid-search/search?searchQuery=0000-0002-8985-2650
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=57448533900

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