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PECULIARITIES OF DEVELOPMENT OF THE HUMAN FACIAL REGION OF SKULL4

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Summary.

Introduction. *Elucidation of the peculiarities of the morphogenesis of the structures of the human maxillofacial region does not lose its relevance among scientists-anatomists, embryologists, maxillofacial and pediatric surgeons, which is explained by a rather large congenital pathology of the structures of the human face, which rank third among all congenital malformations (CMF). Morphological studies of the sources of rudiments and the chronological sequence of the appearance of the bones of the facial part of the human head, clarifying the critical periods of their development will contribute development of new and improvement of existing methods of early diagnosis and effective surgical correction of CMF of the face.*

The aim of the study. *The aim of this paper was to clarify the sources, to find out the chronological sequence of the appearance of rudiments and the peculiarities of the morphogenesis of the bones of the facial part of the human skull.*

Material and methods. *Specimens of 20 embryos and 25 human pre-fetuses aged from 4 to 12 weeks of intrauterine development (IUD) (4.0-80.0 mm parietal-coccygeal length (PCL)) were studied. A complex of classical and modern methods of morphological research is applied: making and studying a series of consecutive histological sections, microscopy, morphometry, three-dimensional reconstruction.*

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 higher education "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. *Sources of facial structures – mesenchyme of five facial evaginations (frontal process, paired mandibular and hyoid branchial arches) are determined on specimens of 4-week aged human embryos. At the end of the 4th week of IUD, two processes of the mandibular branchial arch are visible – maxillary and mandibular, and the brain is surrounded by an ectomeningeal capsule, the source of which is mesenchyme of neuroectodermal origin. Its outer layer (ectomeninx) forms the splanchnocranium – the rudiment of the bones of the facial part of the skull, which ossifies in both a membranous and cartilaginous way. In the 5th week of IUD, the process of fusion of the derivatives of facial evaginations begins. In the 6th week of IUD, the mandibular processes of the I branchial arch merge along the midline, forming the rudiment of the mandible. At the 7th week of IUD, the ectomeningeal capsule differentiates into a cartilaginous structure, which at the 8th week of IUD becomes continuous around the brain and gives the sources of the bones of the base of the skull and the cartilaginous nasal capsule. The nasal capsule is the source of development of the ethmoid bone, nasal septum, and lower concha. At the 7th week of IUD the maxillary, medial, and lateral nasal processes connect with each other, which leads to the completion of the morphogenesis of the maxilla. In the 8th week of IUD, the center of ossification is first detected in the suprabrow region of the frontal bone rudiment. In the 9th week of IUD, active processes of osteogenesis occur in the mandible, as a result of which its base is formed, while the coronal and condylar processes are ossified by cartilaginous osteogenesis from secondary centers that appear after the 10th week of IUD. Each nasal bone ossifies from one cartilaginous center at the beginning of the 9th week of IUD, and the lacrimal bones ossify from one membranous center during the 12th week of IUD.*

Conclusions.

1. Disruption in the processes of proliferation, fusion and transformation of the branchial apparatus at the 5-6th weeks of intrauterine development leads to the appearance of severe defects, in particular, cleft upper lip, alveolar process and palate.

2. The condensed mesenchyme of the front part of the ectomeningeal capsule (in front of the pituitary gland) has a neuroectodorsal origin, and its outer layer (ectomeninx) forms the splanchnocranium – the source of the bones of the facial part of the skull (frontal, lacrimal, zygomatic, nasal bones, vomer, maxilla and mandible), and ossifies in both a membranous and cartilaginous way.

3. The frontal, lacrimal, nasal bones, vomer, as well as the premaxillary part of the maxilla (incisive bone) originate from the mesenchyme of the mandibular branchial arch. The maxilla and the zygomatic bone originate from the mesenchyme of the maxillary process, while the mandible and the tympanic part of the temporal bone originate from the mesenchyme of the mandibular process of the 1st branchial arch.

4. Time intervals during which active proliferative changes and differentiation of embryos occur (7 and 10 weeks of human prenatal development) can be classified as critical periods of development of bone rudiments of the human skull with the possible appearance of congenital malformations.

Key words: *Embryonic Development; Facial Part of the Skull; Membranous and Cartilaginous Osteogenesis; Human.*

Introduction

Elucidation of the features of the morphogenesis of the structures of the human maxillofacial area does not lose its relevance among anatomists, embryologists, maxillofacial and pediatric surgeons. The high interest in this topic is explained by the rather large congenital pathology of the structures of the human face, which rank third among all congenital malformations (CMF). Of these, 70% are congenital cleft upper lip and palate, and 30% are various forms of craniosynostosis and craniofacial dysostosis [1-6]. The number of children with CMF of the face and jaws tends to increase [6, 7]. In particular, CMF in the form of clefts of the upper lip and palate occur in approximately 10% of all human congenital pathology [9, 10]. The highest risk of mortality is in children with complex CMF affecting several organ systems [11]. Some of the syndromes may require lifelong treatment of patients in adulthood, which impairs the quality of life. Congenital deformity of the mandible, which may be a consequence of Robin's syndrome, improper development of the first branchial arch, or Treacher-Collins syndrome [9], requires performing straight, curved, or linear osteotomies. Ankylosis in the region of the temporomandibular joint is a potential etiological factor of impaired growth of the mandible and subsequent facial asymmetry in children [8]. Children with postnatally diagnosed severe hypoplasia of the maxilla or mandible are treated with an autograft of the iliac bone or a rib-cartilage fragment accompanied by distraction osteogenesis [12]. Congenital hypoplasia of the mandible most often occurs as a result of underdevelopment of the branchial apparatus, which occurs unilaterally or bilaterally [13]. Congenital intranasal encephaloceles are CMF bones of the skull, associated with complex genetic syndromes or associated dysmorphisms, which today are treated using the transnasal endoscopic method [14, 15]. It is well known that despite the dominance of genetic factors, the occurrence and development of defects are quite sensitive to the influence of modifying harmful environmental factors [15, 16]. Particularly severe cosmetological and socially adaptive consequences can occur with CMF of the bones of the facial part of the skull (maxilla, mandible, lacrimal, nasal, palatine, zygomatic bones, vomer and lower nasal conchae). Morphological studies of the sources of the rudiments and the chronological sequence of the appearance of the bones of the facial part of the human head, clarifying the critical periods of their development will contribute development of new and improvement of existing methods of early diagnosis and effective surgical correction of face CMF [18].

The aim of the study. The aim of this paper was to clarify the sources, to find out the chronological sequence of the appearance of rudiments and the peculiarities of the morphogenesis of the bones of the facial part of the human skull.

Material and methods

The work is carried out within the framework of the initiative research work of the Department of Histology, Cytology and Embryology of Institution of higher education “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.

Specimens of 20 embryos and 25 human pre-fetuses aged from 4 to 12 weeks of intrauterine development (IUD) (4.0-80.0 mm parietal-coccygeal length (PCL)) from the archival funds of the Department of Histology, Cytology and Embryology of the Bukovinian State Medical University were studied. The periods of IUD are systematized by parietal-coccygeal length according to the classification of B.P. Khvatov and Yu.N. Shapovalov (1969). A complex of classical and modern methods of morphological research is applied: making and studying a series of consecutive histological sections, microscopy, morphometry, three-dimensional reconstruction.

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.

Results and their discussion

Based on our material, it was found that the bones of the facial part of the skull arise from the mesenchyme of five facial protrusions, which are clearly visible on three-dimensional computer reconstructions of 4-week-old human embryos. The sources of development of facial structures are the frontal process, paired mandibular and hyoid branchial arches. At the end of the 4th week of IUD, two processes of the mandibular branchial arch are visible – maxillary and mandibular (Fig. 1). All these mesenchymal evaginations surround the stomodeum – the primary oral cavity, which is caudally separated from the primary intestine by the oropharyngeal membrane. The frontal process and branchial arches are covered with ectoderm and contain inside mesenchyme, which is the source of the development of bone, cartilaginous and vascular structures of the facial part of the head.

During this period of IUD, the mesenchyme,

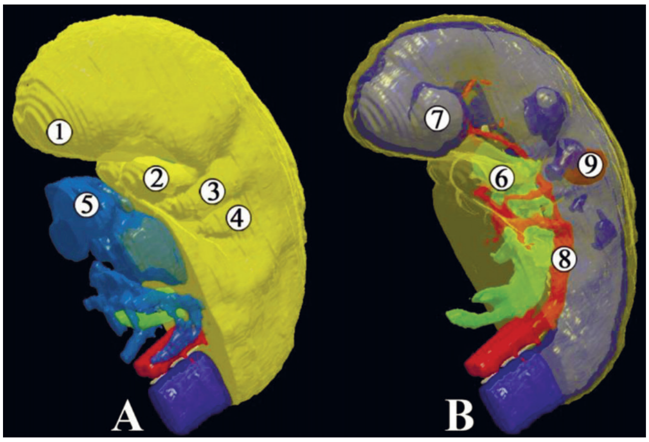


Fig. 1. Three-dimensional computer reconstruction model of the upper half of a human embryo (4.5 mm PCL, 4th week of IUD). Left side projection. A – external contours, B – internal structures. Magnification x12:

1 – frontal process; 2 – maxillary process of the 1st branchial arch; 3 – mandibular process of the 1st branchial arch; 4 – hyoid branchial arch; 5 – heart; 6 – foregut; 7 – cardinal veins; 8 – left dorsal aorta.

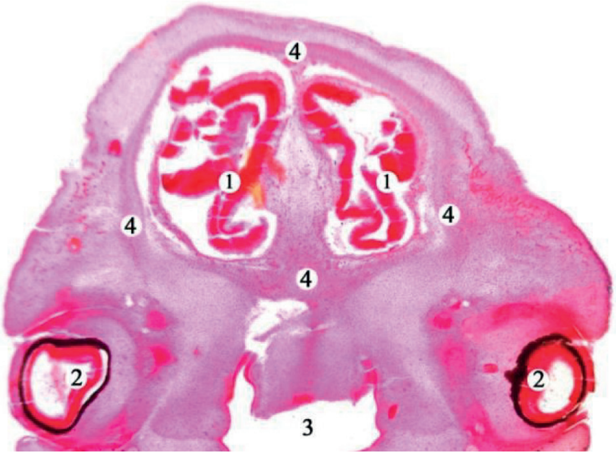


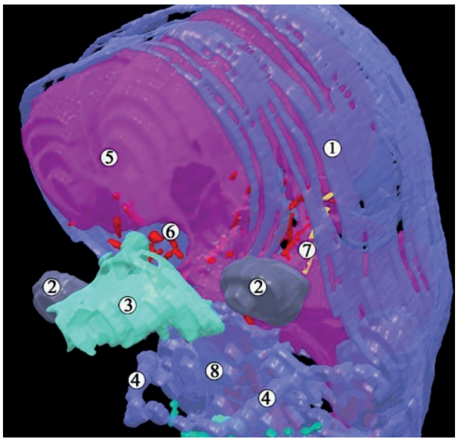
Fig. 2. Frontal section of the head of a 4-week-age human embryo (5.0 mm PCL). Staining with hematoxylin and eosin. Photo of the microspecimen. Magnification x50:

1 – brain; 2 – rudiments of eyeballs; 3 – rudiment of the nasal cavity; 4 – mesenchymal capsule (ectomeninx).

which originates from the neural crest and occipital sclerotomes, surrounds the brain and forms a capsule (Fig. 2). The condensed mesenchyme of the front part of the ectomeningeal capsule (in front of the pituitary gland rudiment) has a neuroectodorsal origin, and its outer layer (ectomeninx) forms the splanchnocranium – the source of the bones of the facial part of the skull (frontal, lacrimal, zygomatic, nasal bones, vomer, maxilla and mandible), and ossifies in both a membranous and cartilaginous way.

In the 5th week of IUD, together with the formation of optic and nasal placodes, the process of fusion of facial protrusions derivates (frontal process, medial and lateral nasal processes of the maxillary process and mandibular process of the 1st branchial arch, and hyoid branchial arch) begins, resulting in nasal pits and primary nasal cavity.

In the 6th week of IUD, the mandibular processes of the 1st branchial arch merge along the midline, forming the rudiment of the mandible. Disruption of the processes of proliferation, fusion and transformation of the branchial apparatus at the 5-6th week of IUD leads to the appearance of severe CMF, in particular, cleft lip.



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1 – brain; 2 – rudiments of eyeballs; 3 – rudiment of the nasal cavity; 4 – mesenchymal capsule (ectomeninx).

At the 7th week of IUD, the differentiation of mesenchymocytes of the ectomeningeal capsule into chondroblasts begins, and at the 8th week of IUD, the cartilaginous rudiment of the skull becomes a continuous structure from which the base of the skull and the cartilaginous nasal capsule (ectoethmoid) develops (Fig. 3). The nasal capsule is the source of development of the ethmoid bone, nasal septum, and lower concha.

The mandible is formed by both membranous and cartilaginous osteogenesis using the Meckel's cartilage model (Fig. 4). The body of the mandible ossifies in a membranous way during the 6-7th week of IUD from independent centers of ossification (mental bones) in the region of future symphysis of the mandible.

In 7-week-age human fetuses 19.0-20.0 mm PCL the maxillary, medial, and lateral nasal processes, connect with each other, which leads to the completion of the morphogenesis of the maxilla. At this stage of IUD, osteogenic islands are rarely observed (compared to the mandible), and cartilaginous rudiments are completely absent.

On the 8th week of IUD, the center of ossification is first detected in the suprabrow area of the frontal bone, slightly above its supraorbital edge. Both segments of the rudiment of the frontal bone are separated by the interfrontal fossa. The frontal, lacrimal, nasal bones, vomer, as well as the premaxillary part (incisive bone) of the maxilla originate from the mesenchyme of the mandibular branchial arch. The maxilla and the zygomatic bone originate from the mesenchyme of the maxillary process, while the mandible and the tympanic part

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of the temporal bone originate from the mesenchyme of the mandibular process of the 1st branchial arch.

In the 9th week of IUD, active processes of osteogenesis occur in the mandible, as a result of which its base is formed, while the coronal and the condylar processes are ossified by cartilaginous osteogenesis from secondary centers that appear after the 10th week of IUD. Bony trabeculae in the mandible, which are located on both ventro-lateral surfaces of Meckel's cartilage, converge with each other in the distal direction. Appositional growth of bone tissue of the mandible in the maxillofacial apparatus gradually forms the front part of the head. Therefore, the mandible has the ability to grow in two directions – along the midline and laterally in the area of the condyles.

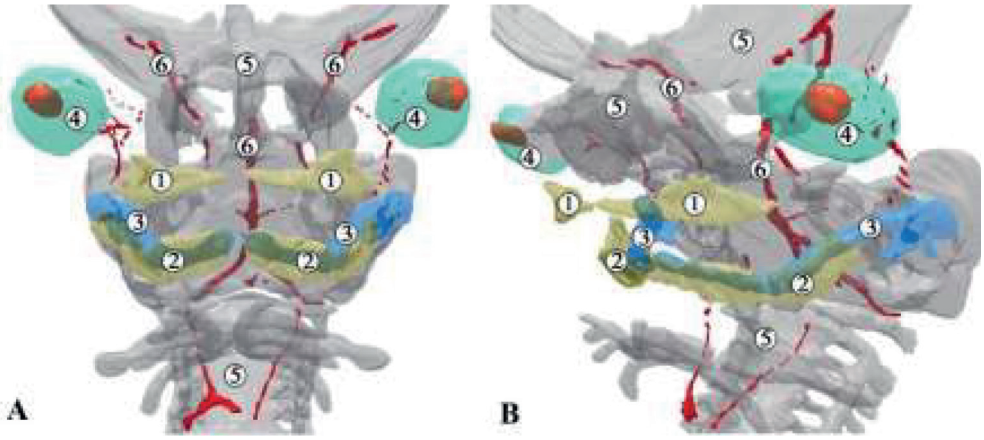

Fig. 4. Three-dimensional computer reconstruction of the upper part of a 7-week-age human prefetus 17.0 mm PCL. A – frontal projection, B – left frontolateral projection. Magnification x12:

1 – bone tissue of the maxilla; 2 – bone tissue of the mandible: 3 – Meckel's cartilage; 4 – eyeballs; 5 – rudiments of the scull bones; 6 – blood vessels.

The lower concha ossifies from one cartilaginous islet during the 5th month of IUD in the region of the lateral part of the nasal capsule. Over time, each lower concha separates from the nasal capsule, forming a separate bone. Each nasal bone ossifies from one cartilaginous center at the beginning of the 9th week of IUD, and the lacrimal bones ossify from one membranous center during the 12th week of IUD.

The nasal septum ossifies in a membranous way, starting from above and behind, forming a perpendicular plate of the ethmoid bone. The cartilage of the nasal septum in human fetuses is not ossified. The vomer ossifies in a layer of connective tissue that covers the lower posterior edge of the cartilaginous nasal septum on both sides. On the 8th week of IUD, ossification centers appear on the sides of the midline, and by the 12th week of IUD, these centers are connected under the cartilage, forming a groove for the cartilage of the nasal septum. Fusion of bony plates progresses forward and upward as the intervening cartilage is slowly resorbed.

The maxilla, zygomatic and palatine bones develops through membranous ossification. Each maxilla ossifies from a single center, which appears in the 6th week of IUD slightly above the canine (Fig. 5). Later, ossification spreads to the rest of the maxilla. The zygomatic bone ossifies from a single center that appears in the 8th week of IUD. Ossification of each palatine bone also occurs on the 8th week of IUD from a single center that appears in the mesenchyme in a perpendicular plate, after which ossification spreads to all parts of the bone.

Until the 10th week of IUD, the frontal reorientation of the orbit is still ongoing, the interorbital distance decreases compared to the width of the facial part of

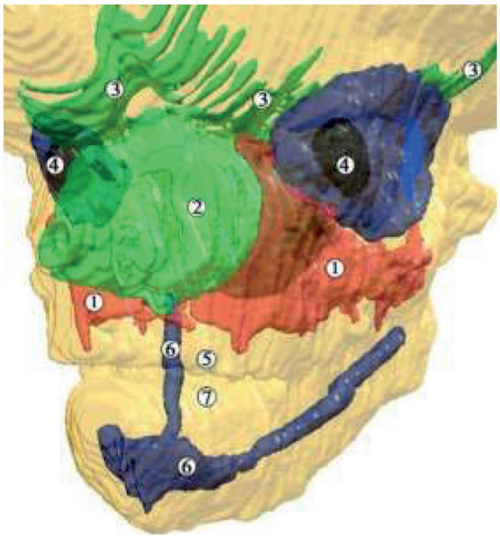

Fig. 5. Three-dimensional computer reconstruction of the 10-week-age human fetus head (48.0 mm PCL). Left anterior-lateral projection. Magnification x10:

1 – maxilla; 2 – nasal capsule; 3 – calvaria bones rudiments; 4 – eyeballs; 5 – soft tissues of the upper lip; 6 – Meckel's cartilage; 7 – soft tissues of the lower lip.

the head. Frontalization of the face contributes to the consolidation of the main facial rudiments, and the face of the prefetuses at this stage of IUD acquires an anthropomorphic appearance. In 10-week-age human fetuses (42.0-52.0 mm PCL), the ossification of the orbital plate of the frontal bone begins in its medial part. During this period, foci of ossification also appear in the lacrimal bone and the orbital plate of the large wing of the sphenoid bone (Fig. 6).

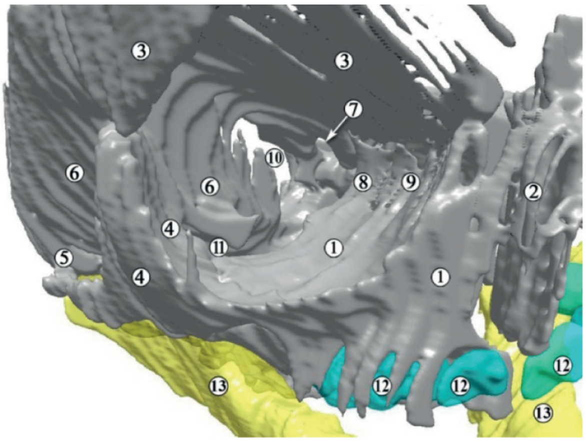

Fig. 6. Three-dimensional computer reconstruction of the right orbit of an 11-week-age human fetus (60.0 mm PCL). Frontal projection. Magnification x25:

1 – maxilla; 2 – nasal bone; 3 – frontal bone; 4 – zygomatic bone; 5 – zygomatic process of the temporal bone; 6 – greater wing of the sphenoid bone; 7 – optic canal; 8 – ethmoidal bone; 9 – lacrimal bone; 10 – superior orbital fissure; 11 – inferior orbital fissure; 12 – teeth rudiments; 13 – mandible.

In human fetuses of the 12th week of IUD, the formation of mandibular processes continues, since they came out of the angles of the mandible in the dorso-cranial direction. The solid base of the branches of the mandible consists of hyaline cartilage, which was gradually replaced by bone tissue.

Obtained data on maxillary processes establishment correlates with study, conducted by the means of ultrasound on prefetuses without congenital malformations as well [17]. Three-dimensional methods for prenatal development investigations (with source information from the sonographic images or histological slides) are considered as the most reliable ones. Our data on stomotodeum and mandible formation differs from other sources, but is still framed within the end of embryological period [19, 20] – it was mentioned in the 5th week of IUD as a period of lower wall of stomodeum formation with mandibular processes fusion. Additionally, the formation of periosteum wasn't detailed included in our studies, but the osteogenetic island formation terms and wide distribution during prefetal period correlates with other papers [17, 19]. The earliest sources of mandibular and maxillary rudiments as branchial arches correlate with other papers [21, 22], as well as approximate time for Meckel's cartilage formation [7, 10, 15] and orbital fossa mesenchymal origination [20, 23-25].

Conclusions.

1. Disruption of the processes of proliferation, fusion and transformation of the gill apparatus at the 5-6th week of intrauterine development leads to the appearance of severe defects, in particular, non-union of the upper lip, cellular process and palate.

2. The condensed mesenchyme of the front part of the ectomeningeal capsule (in front of the pituitary gland) has a neuroectodorsal origin, and its outer layer (ectomeninx) forms the splanchnocranium - the beginning of the bones of the facial part of the skull (frontal, lacrimal, zygomatic, nasal bones, lamina, upper and mandibles), and ossifies in both a membranous and cartilaginous way.

3. The frontal, lacrimal, nasal bones, vomer, as well as the premaxillary part of the maxilla originate from the mesenchyme of the mandibular branchial arch. The maxilla and the zygomatic bone originate from the mesenchyme of the maxillary process, while the mandible and the tympanic part of the temporal bone originate from the mesenchyme of the mandibular process and the branchial arch.

4. Time intervals during which active proliferative changes and differentiation of embryos occur (7 and 10 weeks of human prenatal development) can be classified as critical periods of development of bone embryos of the human skull with the possible appearance of congenital malformations.

Prospects for further research. We consider it expedient to investigate the regularities of the constitutional morphology of the facial part of the head in the postnatal period of human ontogenesis.

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ОСОБЛИВОСТІ РОЗВИТКУ ЛИЦЕВОГО ВІДДІЛУ ЧЕРЕПА ЛЮДИНИ

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Резюме

Вступ. З'ясування особливостей морфогенезу структур щелепно-лицевої ділянки людини не втрачає актуальності серед вчених-анатомів, ембріологів, щелепно-лицевих і дитячих хірургів, що пояснюється досить великою уродженою патологією структур лиця людини, які посідають третє місце серед всіх уроджених вад розвитку (УВР). Морфологічні дослідження джерел закладки та хронологічної послідовності появи кісток лицевого відділу голови людини, з'ясування критичних періодів їх розвитку сприятиме розробці нових та удосконаленню існуючих методів ранньої діагностики та ефективній хірургічній корекції УВР лиця.

Мета дослідження. Уточнити джерела, з'ясувати хронологічну послідовність появи закладок та особливості морфогенезу кісток лицевого відділу черепа людини.

Матеріал і методи дослідження. Досліджено препарати 20 зародків та 25 передплодів людини віком від 4-го до 12-го тижнів внутрішньоутробного розвитку (ВУР) (4,0-80,0 мм тім'яно-куприкової довжини (ТКД)). Застосовано комплекс класичних та сучасних методів морфологічного дослідження: виготовлення та вивчення серій послідовних гістологічних зрізів, мікроскопія, морфометрія, тривимірне реконструювання.

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 Закладу вищої освіти «Буковинський державний медичний університет» на тему «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. На препаратах 4-тижневих ембріонів людини визначаються джерела лицевих структур – мезенхіма п'яти лицевих виступів (лобовий відросток, парні нижньощелепна та під'язикова зяброві дуги). Наприкінці 4-го тижня ВУР помітні два відростка нижньощелепної зябрової дуги – верхньо- та нижньощелепний, а головний мозок оточений ектоменінгеальною капсулою, джерелом якої є мезенхіма нейроектодермального походження. Її зовнішній шар (ектоменінкс) формує спланхнокраніум – зачаток кісток лицевого відділу черепа, який скостеніває як перетинчастим, так і хрящовим шляхом. На 5-му тижні ВУР починається процес зрощення похідних лицевих виступів. На 6-му тижні ВУР нижньощелепні відростки І зябрової дуги зливаються по серединній лінії, утворюючи зачаток нижньої щелепи. На 7-му тижні ВУР ектоменінгеальна капсула диференціюється у хрящову структуру, яка на 8-му тижні ВУР стає безперервною навколо головного мозку і дає зачатки кісток основа черепа та хрящову носову капсулу. Носова капсула є джерелом розвитку решітчастої кістки, носової перегородки та нижньої носової раковини. На 7-му тижні ВУР верхньощелепний, присередній та бічний носові відростки стикаються між собою, що призводить до завершення морфогенезу верхньої щелепи. На 8-му тижні ВУР вперше виявляється центр скостеніння у надбрівній ділянці зачатка лобової кістки. На 9-му тижні ВУР відбуваються активні процеси остеогенезу в нижній щелепі, в результаті яких формується її основа, тоді як вінцевий і виростковий відростки осифікуються шляхом хрящового остеогенезу з вторинних ¬центрів, які з'являються після 10-го тижня ВУР. Кожна носова кістка скостеніває з одного хрящового осередка на початку 9-го тижня ВУР, а слізні кістки осифікується з одного перетинчастого центру протягом 12-го тижня ВУР.

Висновки.

1. Порушення процесів проліферації, злиття та трансформації зябрового апарату на 5-6-му тижнях внутрішньоутробного розвитку призводить до появи тяжких вад, зокрема, незрощення верхньої губи, коміркового відростка та піднебіння.

2. Конденсована мезенхіма передньої частини ектоменінгеальної капсули (попереду від зачатка гіпофіза) має нейроектодерсальне походження, а її зовнішній шар (ектоменінкс) формує спланхнокраніум – зачаток кісток лицевого відділу черепа (лобової, сльозової, виличної¬, носової кісток, леміша, верхньої і нижньої щелеп), і скостеніває як перетинчастим, так і хрящовим шляхом.

3. Лобова, сльозова, носова кістки, леміш, а також передщелепна частина (різцева кістка) верхньої щелепи походять від мезенхіми нижньощелепної зябрової дуги.¬ Верхня щелепа і вилична кістка походять з мезенхіми верхньощелепного відростка, тоді як нижня щелепа і барабанна частина скроневої кістки походять з мезенхіми нижньощелепного відростка І зябрової дуги.

4. Часові проміжки, протягом яких відбуваються активні проліферативні зміни та диференціація зачатків (7 та 10 тижні пренатального розвитку людини) можуть бути класифіковані як критичні періоди розвитку кісткових зачатків черепа людини з можливою появою уроджених вад розвитку.

Ключові слова: ембріональний розвиток; лицевий відділ черепа; перетинчастий і хрящовий остеогенез; людина.

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