Ministry of Health of the Republic of Belarus
Educational Institution
“Gomel State Medical University”

Department of Pathological Anatomy

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METHODICAL GUIDELINES

for conducting a practical class
in the academic discipline “Pathological Anatomy”
for students
of the 3rd year, Faculty of International Students (instruction in English),
enrolled in the specialty
7-07-0911-01 “General Medicine”

Topic: “Congenital malformations”

Duration: 3 hours

Approved at the meeting of the Department of Pathological Anatomy
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EDUCATIONAL AND INSTRUCTIONAL GOALS, OBJECTIVES, AND MOTIVATION FOR MASTERING THE TOPIC

Educational Goal:

- To analyze the main periods of human embryonic development. To examine in detail the nature of dysembryogenesis during various developmental periods. To define the teratogenic termination period and provide examples. To study the etiopathogenesis of congenital malformations and the mechanisms of teratogenesis. To review the principles of classification of congenital malformations (CM). To provide examples of the most common congenital malformations of various organs and systems, and to know the clinical manifestations of chromosomal disorders.

Instructional Goal:

- Within the framework of the educational process for this academic discipline, the student must acquire not only theoretical knowledge, practical skills and abilities in the specialty but also develop their personal potential. They should cultivate qualities of responsibility and patriotism, be prepared to actively participate in the economic, socio-cultural, and public life of the country, recognize the social significance of their future professional activity, understand the norms of medical ethics and deontology, and learn to observe academic and labor discipline. In the course of studying the educational material, students should realize the importance of maintaining a healthy lifestyle and, as an example in the future, when performing professional duties, set an example for those around them and their patients.

Objectives: Upon completion of the practical session, the student must:

***Know*:**

- The definition of congenital malformations;
- The main periods of embryonic development and the nature of dysontogenesis at different time intervals;
- The mechanisms of teratogenesis;
- The basic concepts used in teratology;
- The etiology of congenital malformations;
- The morphological manifestations of congenital malformations of the central nervous system, cardiovascular system, genitourinary system, respiratory system, and digestive system;
- Chromosomal disorders and twin malformations.

Be able to:

- Identify major general pathological processes and diseases using histological specimens under light microscopy;
- Diagnose pathological processes and diseases based on the description of macroscopic and microscopic changes in organs and tissues of the body.

***Master*:**

- Basic techniques for working with a microscope;
- Skills in clinical-anatomical analysis;

- The fundamentals of synthetic generalization of morphological diagnostic signs of diseases and their correct interpretation in cause-and-effect relationships.

Motivation for Mastering the Topic:

Mastering the materials of this topic is a necessary prerequisite for understanding the patterns of morphological reactions and their clinical manifestations in congenital malformations, which occupy a leading role in the structure of morbidity. This knowledge is also necessary in the future professional activity of a physician for the clinical evaluation of conclusions made by a pathologist, for the clinical diagnosis and treatment of diseases, as well as for analyzing the sources of diagnostic errors in clinical practice.

QUESTIONS

1. Congenital malformations of the placenta. Etiology. Pathogenesis. Morphology. Clinical manifestations. Complications and outcomes.
2. Congenital malformations of the amnion. Etiology. Pathogenesis. Morphology. Clinical manifestations. Complications and outcomes.
3. Congenital malformations of the umbilical cord. Etiology. Pathogenesis. Morphology. Clinical manifestations. Complications and outcomes.

COURSE OF THE SESSION

Congenital malformations, also referred to as birth defects, congenital anomalies, or congenital disorders, are defined as structural, functional, or metabolic abnormalities that are present at birth. These anomalies result from defects in morphogenesis, histogenesis, or biochemical pathways during embryonic or fetal development. They may be macroscopic, presenting as gross structural defects, or microscopic, involving cellular or molecular alterations. Etiologically, congenital malformations can be genetically determined, environmentally induced, or multifactorial in origin.

Teratogens disrupt normal development through several basic pathogenic mechanisms at the cellular and tissue level. These include mutations that alter gene structure or expression, as seen with alkylating agents, and chromosomal aberrations, both numerical (aneuploidy) and structural (deletions, translocations). Teratogens may also cause mitotic interference, inhibiting cell division via spindle poisons such as colchicine, or alter cell differentiation by disrupting gene expression without direct mutation, as observed with retinoids affecting Hox genes. Excessive apoptosis, or programmed cell death beyond physiological limits, leads to tissue hypoplasia or aplasia. Impaired cell migration results in heterotopias or fusion defects, exemplified by neural tube defects due to folate deficiency. Mechanical disruption, such as amniotic bands causing amputations or constriction rings, and vascular disruption leading to ischemia, hemorrhage, or thrombosis with subsequent tissue necrosis (e.g., bowel atresia), represent additional important mechanisms.

The critical period, also known as the sensitive period, is a specific time window during embryogenesis when a particular organ or structure is most susceptible to teratogenic insult. During this period, the organ undergoes rapid differentiation and morphogenesis. Before the critical period, in the pre-differentiation phase, teratogens typically follow an "all-or-none" principle, meaning exposure results either in embryonic lethality or no observable effect. After the critical period, teratogens usually cause functional or growth disturbances rather than structural malformations. The teratogenic termination period refers to the latest developmental stage at which a teratogen can induce a specific structural malformation; beyond this point, the same teratogen may cause only physiological or minor morphological defects. For most major organs, the termination period ends by the 8th to 10th week of gestation, corresponding to the end of the embryonic period. Illustrative examples of critical periods include neural tube closure between days 21 and 28 post-fertilization, cardiac development from days 20 to 50, palate closure during weeks 7 to 9, and external genitalia development between weeks 7 and 14.

The etiology of congenital malformations is classically divided into three major categories, although overlap frequently occurs. Genetic causes account for approximately 15–25% of cases and include chromosomal abnormalities such as

trisomies, monosomy X, and deletions, as well as single-gene mutations responsible for Mendelian disorders like achondroplasia or Marfan syndrome. Environmental factors contribute to about 8–12% of cases and encompass physical agents such as ionizing radiation and hyperthermia; chemical teratogens including alcohol, valproic acid, thalidomide, isotretinoin, warfarin, and phenytoin; infectious agents of the TORCH complex (Toxoplasma, Rubella, Cytomegalovirus, Herpes simplex, Zika virus); and maternal metabolic disorders such as pregestational diabetes mellitus and phenylketonuria. Multifactorial inheritance, accounting for approximately 20–25% of cases, involves the interaction of genetic predisposition (polygenic) with environmental triggers; most common isolated malformations, including neural tube defects, cleft lip with or without cleft palate, and congenital heart defects, fall into this category. Despite thorough evaluation, no specific etiology is identified in approximately 40–50% of cases.

Basic terminology in teratology distinguishes several types of structural anomalies. A malformation is a primary structural defect due to an intrinsically abnormal developmental process, such as cleft lip. A disruption is a structural defect resulting from the breakdown of previously normal tissue, exemplified by the amniotic band sequence. A deformation is an alteration in form or position caused by mechanical forces, as seen in clubfoot due to oligohydramnios. Dysplasia refers to the abnormal organization or differentiation of cells within a specific tissue type, such as in skeletal dysplasias. Congenital malformations are classified as isolated or single when only one organ system is affected, for example, a ventricular septal defect. Multiple malformations, where two or more malformations occur in one individual, are further categorized. A syndrome is a recognizable pattern of anomalies with a single known etiology, such as Down syndrome. A sequence is a cascade of anomalies triggered by a single initial defect, typified by Potter sequence (renal agenesis leading to oligohydramnios, which in turn causes pulmonary hypoplasia and facial compression anomalies). An association is the non-random occurrence of multiple malformations without a known common etiology, with VACTERL association (Vertebral, Anal, Cardiac, Tracheo-Esophageal, Renal, Limb) being a classic example. A spectrum describes variable expression of the same underlying disorder.

Multiple Congenital Anomaly (MCA) syndromes are conditions in which an individual presents with two or more major or minor malformations affecting different organ systems, all causally related to a single underlying etiological factor, which may be genetic, chromosomal, or environmental. Common examples include Down syndrome (trisomy 21), Patau syndrome (trisomy 13), CHARGE syndrome (Coloboma, Heart defects, Atresia choanae, Retarded growth, Genital hypoplasia, Ear anomalies, typically due to CHD7 mutation), VATER or VACTERL association, and fetal alcohol syndrome.

Phenotypic Characteristics of Down Syndrome and Patau Syndrome.

Feature	Down Syndrome (Trisomy 21)	Patau Syndrome (Trisomy 13)
Craniofacial	Brachycephaly, flat occiput, upslanting palpebral fissures, epicanthal folds, Brushfield spots (iris speckling), flat nasal bridge, small ears, protruding tongue, short neck with redundant skin.	Microcephaly, sloping forehead, scalp defects (cutis aplasia), microphthalmia / anophthalmia, hypotelorism or cyclopia, cleft lip and palate (bilateral, midline), low-set malformed ears, capillary hemangiomas.
Limb	Brachydactyly, clinodactyly of 5th finger (incurved), single transverse palmar crease (simian crease), increased gap between 1st and 2nd toes (sandal gap).	Polydactyly (postaxial, usually hands), flexed overlapping fingers, rocker-bottom feet (prominent calcaneus).
Visceral / Neurological	Congenital heart defects (AV canal most common), duodenal atresia, Hirschsprung disease, hypotonia, intellectual disability (mild to moderate), increased risk of leukemia.	Holoprosencephaly (midline forebrain defect), neural tube defects, congenital heart defects (VSD, ASD, dextroposition), cystic kidneys, omphalocele, genital anomalies (cryptorchidism, bicornuate uterus).
Other	Single umbilical artery, intellectual disability (IQ 30–50).	Profound intellectual disability, early lethality (median survival <1 year).

Phenotypic Characteristics of Fetal Alcohol Syndrome (FAS).

Fetal alcohol syndrome is a teratogenic multiple congenital anomaly syndrome caused by maternal ethanol consumption during pregnancy. The phenotype is defined by a classic triad of features. First, prenatal and postnatal growth deficiency is observed, characterized by low weight, length, and head circumference (microcephaly) with poor catch-up growth. Second, characteristic facial dysmorphisms, which are the most specific findings, include short palpebral fissures (short horizontal length of the eye opening), a smooth philtrum (flattened or absent ridges), and a thin vermilion border of the upper lip. Additional craniofacial features may include epicanthal folds, a flat nasal bridge, micrognathia in infancy, and hypoplastic midface. Third, central nervous system abnormalities are present, encompassing structural defects such as microcephaly, agenesis of the corpus callosum, and cerebellar hypoplasia; neurological findings including hypotonia, poor coordination, and fine motor deficits; and functional impairments such as intellectual disability, learning disabilities, attention deficits resembling ADHD, executive dysfunction, and social or behavioral problems with poor impulse control. Other associated features include cardiac defects (ventricular septal defect, atrial septal defect), renal anomalies, joint contractures, radioulnar synostosis, and hearing loss.

Major Congenital Malformations of Individual Organs and Systems.

System	Major Malformations
Cardiovascular	Ventricular septal defect (VSD), Atrial septal defect (ASD), Tetralogy of Fallot, Transposition of the great arteries (TGA), Coarctation of the aorta, Hypoplastic left heart syndrome (HLHS), Atrioventricular canal defect (AV canal).
Central Nervous System	Neural tube defects: Anencephaly, Myelomeningocele (spina bifida cystica), Encephalocele; Holoprosencephaly, Hydrocephalus (aqueductal stenosis), Dandy-Walker malformation, Agenesis of corpus callosum, Lissencephaly.
Gastrointestinal	Cleft lip with or without cleft palate, Cleft palate alone, Esophageal atresia with/without tracheoesophageal fistula (TEF), Duodenal atresia, Jejunoileal atresia, Imperforate anus (anal atresia), Omphalocele, Gastroschisis, Hirschsprung disease (aganglionic megacolon).
Genitourinary	Renal agenesis (unilateral/bilateral), Horseshoe kidney, Polycystic kidney disease (autosomal recessive or dominant), Ureteropelvic junction (UPJ) obstruction, Posterior urethral valves (males), Hypospadias, Bladder exstrophy, Cloacal exstrophy.
Musculoskeletal	Clubfoot (Talipes equinovarus), Developmental dysplasia of the hip (DDH), Polydactyly, Syndactyly, Limb reduction defects (e.g., amelia, phocomelia), Skeletal dysplasias (e.g., Achondroplasia, Osteogenesis imperfecta), Congenital scoliosis (hemivertebrae).
Respiratory	Congenital diaphragmatic hernia (CDH – most commonly Bochdalek type), Pulmonary hypoplasia, Congenital cystic adenomatoid malformation (CCAM), Pulmonary sequestration, Tracheal stenosis or atresia.

INFORMATIONAL AND METHODOLOGICAL PART

MAIN LITERATURE

1. Pathomorphology : textbook / ed. by I.V. Sorokina, V.D. Markovskyi, D.I. Halata. - 2nd ed. - Kyiv : AUS Medicine Publishing, 2020. - 327 p., [10] col. inserts : tab.

2. Klatt, E. C. Robbins and Cotran Atlas of Pathology : [with Student Consult Online Access] / Edward C. Klatt. - third edition. - Philadelphia : Elsevier, 2015. - 587 p. : il.

3. Robbins Basic pathology / [ed. by] Vinay Kumar, Abul K. Abbas, Jon C. Aster. - 9th ed. - [Philadelphia] : Elsevier ; Saunders. - 910 p. : ill., scheme, tab.

ADDITIONAL LITERATURE

1. Sobotta. Atlas of human anatomy. [V. 1]. General anatomy and musculoskeletal system / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 400 p. : ill., col. ill.

2. Sobotta. Atlas of human anatomy. [V. 2]. Internal organs / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 259 p. : ill., col. ill.

3. Sobotta. Atlas of human anatomy. [V. 3]. Head, neck, and neuroanatomy / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 370 p. : ill., col. ill.

4. Weir & Abrahams' imaging atlas of human anatomy / ed.: J. D. Spratt [and oth.] ; consultant eds.: J. Weir, P. H. Abrahams. – 5th ed. - [S.l.] : Elsevier, 2017. - xvi, 263 p. : ill.

NORMATIVE LEGAL ACTS AND DOCUMENTS

1. Order of the Ministry of Health of the Republic of Belarus No. 111 of 06/01/1993 "On further improvement of the pathological service of the Republic of Belarus"

Access mode: http://patan.by/menyu/administrativnyie-proczeduryi.html - The date fccess: 20.03.2022.

ELECTRONIC DATABASES

1. Physician's consultant. Electronic Medical Library = Consultant of the doctor. Electronic medical library [Electronic resource] / Publishing group "GEOTAR-Media", LLC "IPUZ". – Access mode: http://www.rosmedlib.ru/ . – Access date: 03/15/2022.

2. Springer Link [Electronic resource] / Springer International Publishing AG. – Access mode: https:link.springer.com. – Date of access: 03/15/2022.