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Pathological anatomy of protein and carbohydrate metabolism disorders.

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1. The purpose of the lesson. To study the issues of etiology, pathogenesis, morphology, complications and outcomes of disorders of carbohydrate and pigment metabolism; to study the morphological features of pathological accumulation of endogenous and exogenous products; to characterize the morphological manifestations of hyaline changes.
2. Requirements for the level of the student for mastering the discipline - pathological anatomy.

The theoretical basis.

I. <u>Parenchymal protein dystrophies.</u>

The essence of parenchymal dysproteinosis consists in changing the physicochemical and morphological properties of cell proteins: they undergo denaturation and coagulation, or, conversely, colliquation, which leads to hydration of the cytoplasm; in cases where the bonds of proteins with lipids are disrupted, destruction of the cell membrane structures occurs. As a result of these disorders, coagulation (dry) or colliquation (wet) necrosis may develop. Parenchymal dysproteinosis includes:

a) Hyaline drip,
b) Hydropic,
c) Horny,
d) Grainy.

Hyaline droplet dystrophy.

With hyaline droplet dystrophy, large hyaline-like protein drops appear in the cytoplasm, merging with each other and filling the cell body; in this case, the destruction of ultrastructural elements of the cell occurs. In some cases, hyaline droplet dystrophy ends with focal coagulation cell necrosis. This type of dysproteinosis is often found in the kidneys, rarely in the liver, and very rarely in the myocardium.

Hydropic dystrophy.

Hydropic, or dropsy, dystrophy is characterized by the appearance in the cell of vacuoles filled with cytoplasmic fluid. It is observed more often in the epithelium of the skin and renal tubules, in hepatocytes, muscle and nerve cells, as well as in the cells of the adrenal cortex.

Horny dystrophy.

Horny dystrophy, or pathological keratinization, is characterized by excessive formation of horny substance in the keratinizing epithelium (hyperkeratosis, ichthyosis) or the formation of horny substance where it normally does not exist (pathological keratinization on the mucous membranes, or leukoplakia, the formation of "cancer pearls" in squamous cell carcinoma). The process can be local or widespread.

<u>Stromal-vascular protein dystrophies.</u>

Stromal-vascular dysproteinosis includes:
a) Mucoid swelling,
b) Fibrinoid swelling (fibrinoid),
c) Hyalinosis,
d) Amyloidosis.

Mucoid swelling.

Mucoid swelling is a superficial and reversible disorganization of the connective tissue. At the same time, the accumulation and redistribution of glycosaminoglycans occurs in the main substance due to an increase in the content of primarily hyaluronic acid. Glycosaminoglycans have hydrophilic properties, their accumulation leads to an increase in tissue and vascular permeability. As a result, plasma proteins (mainly globulins) and glycoproteins are mixed with glycosaminoglycans. Hydration and swelling of the main interstitial substance develop.

Fibrinoid swelling (fibrinoid).

Fibrinoid swelling is a deep and irreversible disorganization of the connective tissue, which is based on the destruction of its main substance and fibers, accompanied by a sharp increase in vascular permeability and the formation of fibrinoid.

Fibrinoid is a complex substance, which includes proteins and polysaccharides of disintegrating collagen fibers, basic substance and blood plasma, as well as cellular nucleoproteins. Histochemically, fibrinoid is different for various diseases, but fibrin is an essential component of it.

Hyalinosis.

With hyalinosis (from the Greek hyalos - transparent, vitreous), or hyaline dystrophy, homogeneous translucent dense masses (hyaline) resembling hyaline cartilage are formed in the connective tissue. The tissue becomes denser, therefore hyalinosis is considered as a type of sclerosis.

Hyalin is a fibrillar protein. In an immunohistochemical study, it detects not only plasma proteins, fibrin, but also components of immune complexes (immunoglobulins, complement fractions), as well as lipids. Hyaline masses are resistant to acids, alkalis, enzymes, PIC-positive, accept acidic dyes (eosin, sour fuchsin) well, and turn yellow or red with picrofuchsin.

Hyaline changes.

They are characterized by the appearance of a substance (intra- or extracellular) with a homogeneous hyaline-like pink coloration when using hematoxylin and eosin. The accumulation of intracellular hyaline deposits in classical morphology is called hyaline droplet dystrophy)), which is most often observed in the epithelium of the renal tubules in diseases accompanied by increased permeability of the glomerular filter (nephrotic syndrome in patients with glomerulonephritis, renal amyloidosis). With alcoholic hepatitis, primary biliary and Indian childhood cirrhosis of the liver (alcoholic hyaline) are found. Extracellular hyaline is found in connective tissue hyalinosis in old scars, foci of sclerosis, in the outcome of fibrinoid necrosis, in arterial walls in arterial hypertension and diabetes mellitus, heart valves in rheumatic disease.

Amyloidosis.

Amyloidosis (from Latin amylum - starch), or amyloid dystrophy, is stromal-vascular dysproteinosis, accompanied by a profound violation of protein metabolism, the appearance of an abnormal fibrillar protein and the formation of a complex substance amyloid in the interstitial tissue and vascular walls.

Amyloid is a protein that is deposited between cells in various tissues and organs. Protein recognition in the clinic depends solely on its detection in biopsies. In light-optical examination using traditional stains, amyloid looks like an amorphous, eosinophilic, hyaline-like intercellular substance, as a result of the progressive accumulation and pressure of which, cell atrophy develops. In order to distinguish amyloid from other deposits (collagen, fibrin), a number of histochemical methods are used, for example, staining with Congo red. In a polarizing microscope, the amyloid is greenish in color, giving birefringence.

Despite the fact that all deposits have the same appearance and tinctorial properties, amyloid is chemically heterogeneous. There are two main and several minor biochemical forms. They are formed with the participation of various pathogenetic mechanisms. Apparently, amyloidosis is a group of diseases, the main feature of which is the deposition of similar substances of protein structure.

In an electron microscope, amyloid consists of unbranched fibrils about 7.5-10.0 nm long (F-component). This structure is the same for all types of amyloidosis. Crystallography and infrared spectroscopy revealed a characteristic folded structure of the shell. This structural feature explains the appearance of birefringence. In addition, the second component (P), which has a pentagonal structure, was revealed in smaller amounts.

Approximately 95% of amyloid consists of fibrillar protein, the remaining 5% is from the glycoprotein P-component.

Among 15 different biochemical variants of amyloid protein, two main ones are distinguished: amyloid from light chains (AL), which is produced by plasma cells (immunocytes), it contains immunoglobulin light chains; bound amyloid (AA) is a unique non-immunoglobulin protein synthesized in the liver.

Other proteins are also found in amyloid deposits. Trans-thyretin is a normal serum protein that binds and transports thyroxine and retinol. The mutant form of transthyretin (and its fragments) are detected in genetically determined diseases called familial amyloid polyneuropathy. Amyloid transthyretin (ATTR) differs from normal transthyretin by a single amino acid residue in the molecule.

P2-Amyloid is a peptide that makes up the nucleus of brain plaques in Alzheimer's disease. It is formed from the largest transmembrane glycoproteins, the so-called amyloid precursor protein (APP). There are also amyloid deposits formed from various precursors such as hormones (procalychitonin) and keratin.

The P-component differs from amyloid fibrils, but is closely associated with them in all forms of amyloidosis. It has structural homology to C-reactive protein. The serum P-component has an affinity for amyloid fibrils and is necessary for the formation of deposits in tissues.

The classification of amyloidosis is based on the chemical structure of the amyloid molecule (AL, AA, ATTR) and clinical syndromes. Amyloidosis can be systemic (generalized) with damage to several organ systems or local, when deposits are found in only one organ. Systemic (generalized) amyloidosis is primary, if it is associated with dyscrasia of immunocytes, or secondary, when it occurs as a complication of chronic inflammation or destructive processes in tissues. Congenital (familial) amyloidosis is a separate heterogeneous group.

Dyscrasia of immunocytes with amyloidosis (primary amyloidosis) is a type of amyloidosis usually systemic, characterized by the presence of AL-amyloid and accounts for about 75% of all amyloidosis. This type of amyloidosis is based on the development of plasma cell dyscrasia. It occurs in patients with multiple myeloma, which is characterized by osteolytic damage to the skeleton. A necessary, although not sufficient, condition for the development of amyloidosis is the presence of the Bens-Jones protein, which has only light chains in the molecule.

Reactive systemic amyloidosis. For amyloidosis of this type, the formation of AA-amyloid is characteristic. It is also called secondary amyloidosis, as it is associated with chronic inflammation, accompanied by tissue destruction. Amyloidosis occurs in tuberculosis, bronchiectasis, and chronic osteomyelitis. Most often, reactive systemic amyloidosis complicates the course of rheumatoid arthritis and other connective tissue diseases such as ankylosing spondylitis, inflammatory bowel disease (especially regional enteritis and ulcerative colitis). Amyloidosis develops in approximately 3% of patients with rheumatoid arthritis.

Amyloidosis associated with hemodialysis occurs after prolonged hemodialysis, carried out in connection with renal failure, and due to the loss of p2-microglobulin. The latter is found in large quantities in the serum of patients with kidney disease, since it is not filtered through dialysis membranes. In about 70% of patients, amyloid deposits are detected in the synovium of the joints and tendons.

Congenital familial amyloidosis is a relatively rare condition that occurs in certain geographic areas. The most fully studied autosomal recessive variant of familial amyloidosis, which is called familial Mediterranean fever. It is characterized by attacks of fever accompanied by inflammation of the serous membranes, including the peritoneum, pleura, and synovial membranes. In this disease, amyloid is represented by the AA variant.

In contrast to the autosomal recessive variant, autosomal dominant familial amyloidosis is characterized by amyloid prolapse mainly in the peripheral nerves. In all these diseases, amyloid fibrils are composed of ATTR.

Localized amyloidosis. Amyloid deposits are usually in the form of nodules, detectable only microscopically and, as a rule, in only one organ. Tumor-like deposits of amyloid are most commonly found in the lungs, larynx, skin, bladder, tongue, and around the eyes. Often on the periphery of amyloid masses, infiltration by lymphocytes and plasma cells is found, which is regarded as a response to amyloid prolapse. In some cases, amyloid is composed of an AL protein and is of immunocytic origin.

Endocrine amyloidosis. Microscopic deposits of amyloid are sometimes found in some endocrine tumors, such as medullary carcinoma, pancreatic islet tumors, pheochromocytoma, poorly differentiated gastric carcinomas, and in pancreatic islets (islets of Langerhans) in type 11 diabetes mellitus. In these cases, amyloidogenic proteins are derived from polypeptide hormones, such as pancreatic islet amyloid polypeptide (1APP).

Senile amyloid. With aging, there are two types of amyloid deposits. Senile cardiac amyloidosis is characterized by the loss of amyloid in the heart of elderly patients (usually in the 8-9th decade of life). It

occurs in two forms: loss of transthyretin, which damages the ventricles, or loss of atrial natriuretic peptide, which damages the atrium. The disease is usually asymptomatic, but can cause severe cardiac abnormalities. At the same time, amyloid deposits in the lungs, pancreas and spleen are detected. This suggests that senile amyloidosis is a systemic disease.

Senile cerebral amyloidosis develops as a result of deposits of AB2 protein deposits in cerebral blood vessels and plaques in individuals with Alzheimer's disease.

Although the precursors of the two major amyloid proteins have been identified, some aspects of their origin are still unclear. In reactive systemic amyloidosis, prolonged tissue destruction and inflammation are important, leading to an increase in serum AA (SAA) levels in the blood serum. An increased amount of SAA is characteristic of inflammation, but in most cases does not lead to amyloidosis. First, SAA is normally degraded to final soluble products by monocyte enzymes. Those patients who develop amyloidosis seem to have a defect in this enzyme, which leads to incomplete destruction of SAA, and thus an insoluble AA molecule is formed. Conversely, genetically determined structural abnormalities in the SAA molecule themselves cause its resistance to destruction by monocytes. With immunocytic dyscrasia, an excess of light chains of immunoglobulin molecules is found, and amyloid can be formed as a result of proteolysis of these chains. In turn, defective defadation leads to the formation of light chains that are resistant to complete proteolysis.

In familial amyloidosis, the loss of transthyretin in the form of amyloid fibrils is not a consequence of transthyretin overproduction. It is believed that genetically determined damage to the structure "pushes" the formation of transthyretins, which are "prone" to abnormal aphegation and proteolysis.

The cells involved in the conversion of precursor proteins into fibrils are not fully characterized, but macrophages are the main candidates for these functions.

II. Morphology of carbohydrate metabolism disorders.

Carbohydrates detected in cells and tissues using histochemical methods are subdivided into polysaccharides (glycogen), glycosaminoglycans (mucopolysaccharides) and glycoproteins.

Disorders of glycogen metabolism - one of the examples of disorders of carbohydrate metabolism - is most often observed in diabetes mellitus and in hereditary carbohydrate dystrophies - glycogenosis. depot of glycogen in the body - the liver and skeletal muscles, the glycogen of these organs is called "labile glycogen", as it is consumed depending on the needs of the body. Another type of glycogen - glycogen of nerve cells, conducting systems of the heart, aorta, endothelium, epithelial tissues, cartilage, leukocytes - stable glycogen, the content of which does not undergo noticeable fluctuations and which is a necessary component of cells. It is possible to detect glycogen in cells and tissues using histochemical staining with Best carmine. Intracellular accumulation of glycogen is observed with disorders of glucose or glycogen metabolism. In diabetes mellitus, there are: 1) intracellular accumulation of glycogen in the epithelial cells of the distal convoluted tubule: the epithelium becomes high, with a light, foamy cytoplasm, glycogen grains are also found in the lumen of the tubules; 2) the inclusion of glycogen in the nuclei of hepatocytes, which become light ("perforated", "empty" nuclei).

Impaired metabolism of glycoproteins in cells or in the intercellular substance is characterized by the accumulation of mucins and mucoids (the so-called mucous or mucoid substances). Glycoproteins in cells and tissues can be detected by histochemical staining with toluidine blue or methylene blue. Obturation of the excretory ducts of the glands with mucus leads to the development of cysts; obturation of the lumen of the bronchi with mucus can lead to the development of atelectasis and foci of pneumonia.

Hereditary disorders of glycogen metabolism are called glycogenosis. Established II types of glycogenoses, each of which is caused by a deficiency of one of the enzymes involved in glycogen metabolism: type 1 - Gierke's disease, type II - Pompe disease, type III - measles disease, type IV - Andersen's disease, type V - Mark-Ardl syndrome , VI type - Hers's disease, VII type - Thomson's disease, VIII type - Tarui's disease, IX type - Haga's disease, X and XI types. Along with this, there are mixed types of glycogenoses, as well as glycogenoses with an unidentified enzyme defect. Depending on whether the sludge is affected by enzymatic defects in the liver, muscles, or at the same time many organs, there are hepatic, muscular and generalized forms of glycogenosis. The most important sign of pathological accumulation of glycogen in tissues with glycogenosis - the absence of post-mortem glycolysis (in this case,

the absorbed glycogen can be easily extracted with an aqueous solution of formalin, which at the same time becomes cloudy, grayish-white milky species; when alcohol is exposed to this solution, gelatinous masses fall out of it, giving a pronounced brown color with iodine).

Brief description of the five main types of glycogenosis

Type I glycogenosis - Gierke's disease - hepatic form - occurs due to a deficiency of glucose-6-phosphatase. The disease manifests itself in infancy; characteristic: lag in the growth of body weight, vomiting, anorexia, hypoglycemia, periodically ketonemic crises. In the future - proportionally small growth in the pituitary type, the "doll-type" face, hepatomegaly. Causes of death are acidotic coma or infections. Macroscopic picture:

liver - enlarged 3-4 times, its surface is smooth, on the cut, the tissue is pale red with an emphasized pattern of lobules; kidneys - enlarged, swollen, pale, yellowish-red in color with a wide cortical zone; the spleen is not enlarged. Microscopic picture: hepatocytes are sharply enlarged with ("watery" cytoplasm, distinct borders and a nucleus located in the center. The staining for glycogen is sharply positive even after fixation of the material in formalin.

Type II glycogenosis - Pompe disease - generalized form - occurs due to a deficiency of the lysosomal enzyme acid maltase, which leads to the accumulation of glycogen primarily inside the lysosomes of cells of striated and smooth muscles, liver, lungs, spleen, vascular walls, brain, skin ... The course of the disease is unfavorable, death occurs in the 1st year of life from heart or respiratory failure, often from aspiration pneumonia. Macroscopic picture: cardiomegaly, macroglossia, damage to the muscles of the esophagus and pylorus. Microscopic picture: myocardial fibers are swollen, light, sharply contoured, similar to plant cells; in the neuromuscular variant - the accumulation of glycogen in the ganglionic and glial cells of the anterior horns of the spinal cord, spinal and autonomic peripheral nodes, damage to skeletal muscles and especially smooth muscles; the amount of glycogen in the liver and skin increases. Electron microscopic picture: lysosomal and cytoplasmic inclusions associated with cell membranes, containing multiple glycogen particles, the size of inclusions is 0.2-1.5 microns.

Type III glycogenosis, dextrin limit (measles disease) occurs due to the absence of amylo-1, 6-gldcosidase, which leads to a violation of glycogen breakdown - glycogen molecules with short external chains are formed. The disease is characterized by an accumulation of abnormal glycogen (dextrin limit) predominantly in the liver, as well as in skeletal muscle and myocardium. The clinical and morphological picture is similar to that in type 1 glycogenosis, but less pronounced.

Type IV glycogenosis, amylopectinosis (Andersen's disease) is a rare type of glycogenosis, characterized by impaired glycogen synthesis, arising from a defect in the branching enzyme, which normally catalyzes the stepwise synthesis of glycogen branches. The disease manifests itself in late infancy or early childhood in the form of liver cirrhosis, hepato- and splenomegaly, ascites, jaundice, bleeding. Cirrhosis of the liver is small-nodular, with the accumulation of poorly soluble abnormal glycogen in hepatocytes, which is perceived by the body as a foreign body and causes the development of cirrhosis. Glycogen is also accumulated in the histiocytes of the spleen, lymph nodes, in the Kupffer's cells of the liver.

Type V glycogenosis (McArdle disease) is a classic muscle glycogenosis associated with the absence of muscle phosphorylase; characterized by myalgias that occur after muscle tension, stiffness in the joints of the limbs and muscle weakness gradually develop, dark urine (due to myoglobin). The disease develops in childhood (after 10 years). Under the sarcolemma of skeletal muscles, sharply CHIK positive vacuoles are found, individual muscle fibers are hyalinized.

3. Lesson plan.

Macropreparations:

1. Hyalinosis of the spleen capsule - pay attention to the thickness and color of the spleen capsule, the surface condition, mark the area of the capsule thickening, its color and thickness.
2. Hyalinosis and sclerosis of valves in rheumatic heart disease - pay attention to the size of the heart, the thickness of the walls of the ventricles, the size of the heart cavities; the thickness and color of the cusps of the mitral and aortic valves.

3 Kidney amyloidosis - pay attention to the size of the kidney, note the color of the parenchyma of the organ, the absence (blurring) of the border between the cortex and the medulla.
4. Amyloidosis of the spleen - pay attention to the size of the spleen, note the change in color and appearance of the parenchyma of the organ on the cut, the state of the capsule.

Micropreparations:
1. Micropreparation “Protein hyaline drops in the epithelium of the proximal convoluted tubules of the kidney (hyaline-drop dystrophy of the epithelium of the kidney tubules)” (staining with hematoxylin and eosin). Pay attention to the size, shape, color, number of inclusions in the cytoplasm of the epithelium, the state of the nuclei and the size of epithelial cells, the lumen of the tubules.
2. Micropreparation “Hydropic dystrophy of the epithelium of the proximal convoluted tubules of the kidney” (staining with hematoxylin and eosin). Pay attention to the number and size of vacuoles in the cytoplasm, the state of the nuclei and the size of epithelial cells, the lumen of the tubules.
3. Micropreparation “Granular degeneration of the epithelium of the proximal convoluted tubule of the kidney” (staining with hematoxylin and eosin). Pay attention to the presence of granularity in the cytoplasm, the state of the nuclei and the size of epithelial cells, the lumen of the tubules.
4. Micropreparation Hyalinosis of the spleen arteries - pay attention to the decrease in the lumen of the arteriole, to the deposits of a homogeneous substance, to note the localization of the process.
5. Micropreparation "Mucoid swelling of the connective tissue." Stained with hematoxylin and eosin, toluidine blue. Pay attention to the nature of the color of the connective tissue, find areas of metachromasia.
6 Micropreparation “Kidney amyloidosis” (staining with hematoxylin-eosin or staining with Congo-red) - pay attention to the increase in the size of the glomeruli and thickening of the walls of arterioles due to the deposition of a homogeneous acidophilic substance, note the localization of the process.
7. Micropreparation “Spleen amyloidosis” (staining with hematoxylin-eosin). Pay attention to the deposits of a homogeneous acidophilic substance, note the localization of the process. Pay attention to the localization, structure and color of amyloid, the state of the cellular elements of the pulp.
8. Micropreparation “Spleen amyloidosis” (Congo red staining) Pay attention to the deposits of a homogeneous acidophilic substance, note the localization of the process. Pay attention to the localization, structure and color of amyloid, the state of the cellular elements of the pulp. Mark the amyloid color when using Congo red.

Electronograms
1. Electronogram “Balloon dystrophy of hepatocyte”. Pay attention to the state of the cytoplasmic reticulum.
2. Electronogram "Protein hyaline drops in the epithelium of the proximal convoluted tubules of the kidney". Pay attention to hyaline drops in the cytoplasm.

4. QUESTIONS

Choose one correct answer
1. Protein inclusions in the cytoplasm of cells look like:
a) basophilic grains,
b) eosinophilic drops or masses,
c) vacuoles,
d) brown granules,
e) golden granules.
2. A plasma cell with an excessive accumulation of protein is called a body:
a) Kaunsilmen,
b) Mallory,
c) Roussel,
d) Heinz,
e) Pappenheim.
3. With protein starvation, steatosis develops in:
a) liver,
b) kidneys,
in the heart,
d) adrenal glands,
e) spleen.
4. With protein dystrophy and swelling of the epithelium of the proximal kidney tubules, the following clinical syndrome develops:
a) proteinuric,
b) edematous,
c) portal hypertension,
d) nephrotic,
e) hemolytic uremic.

5. Hereditary storage diseases are called:
a) thesaurismoses,
b) systemic,
c) autoimmune,
d) cerebrovascular,
e) immunocomplex.

6. Dye for histochemical detection of amyloid
1) Sudan III
2) sudan black
3) congo red
4) toluidine blue
5) hematoxylin-eosin

7. Amyloidosis can complicate the course
1) lymphocytic leukemia
2) myeloid leukemia
3) multiple myeloma
4) pernicious anemia
5) hemolytic anemia

8. Amyloidosis in periodic illness is
1) primary
2) senile
3) tumor-like
4) acquired
5) hereditary

9. Stages of spleen amyloidosis
1) porphyry
2) ham
3) nutmeg
4) brindle
5) greasy
6) sago

10. A pronounced hydropic dystrophy is called:
1) balloon
2) hyaline
3) fat
4) mucous
5 horny

11. Outcome of hydropic dystrophy:
1) coagulation necrosis
2) mucoid swelling
3) colliquation necrosis
4) reverse development
5) amyloidosis.

5. List of recommended literature:
Basic literature:

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Additional literature:

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