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COMORBIDITY AS A MANIFESTATION OF CONNECTIVE TISSUE DYSPLASIA (CLINICAL CASE DESCRIPTION AND COMMENT)

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Abstract. An extract from the medical history of a 17-year-old teenager with comorbidity is given — pathology of 4 systems, including the digestive, excretory, immune and nervous systems. An attempt was made to find a common link in pathogenesis — the failure of mesenchymal tissue. An additional survey plan has been proposed to confirm this hypothesis. The need for a joint examination of children with comorbid pathology by a group of specialists of the relevant profiles is justified.

Key words*: comorbidity; mesenchymal tissue; digestive organs; urinary system; immunity; nervous system*

КОМОРБИДНОСТЬ КАК ПРОЯВЛЕНИЕ ДИСПЛАЗИИ СОЕДИНИТЕЛЬНОЙ ТКАНИ (ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ И КОММЕНТАРИЙ)

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Резюме. Приведена выписка из истории болезни 17-летнего подростка с коморбидностью — патологией 4 систем, включая пищеварительную, выделительную, иммунную и нервную системы. Сделана попытка найти общее звено патогенеза — несостоятельность мезенхимальной ткани. Предложен план дополнительного обследования для подтверждения этой гипотезы. Обоснована необходимость совместного обследования детей с коморбидной патологией группой специалистов соответствующих профилей.

Ключевые слова*: коморбидность; мезенхимальная ткань; органы пищеварения; мочевыделительная система; иммунитет; нервная система*

The term comorbidity was proposed in 1970 by the American doctor A.R. Feinstein. There is no generally accepted international classification of combined diseases.

Several definitions of this clinical concept have been proposed. Comorbidity is a combination of two or more distinct diseases or syndromes, none of which is a complication of the other, if the frequency of this combination exceeds the probability of a random coincidence. Comorbidity is acute and chronic diseases that are not associated with the diagnosis of the underlying disease that was

the reason for hospitalization [1]. The article published in 2018 by L.B. Lazebnik and Yu.V. Konev proposes to use the following classification criteria: genetic predisposition, localization, type and time of occurrence, gender characteristics, disease profile, social causes, comorbid status, localization, etiology and pathogenesis [2].

In pediatric practice, the most common combinations of pathologies of the heart and kidneys (cardiorenal syndrome) is a combination of diseases of the urinary and digestive systems. Pathology of the respiratory system ranks first in frequency in young children. The narrow specialization adopted in modern medicine, including pediatrics, on the one hand, and the lack of erudition of family physicians (general practitioners), on the other, do not allow us to identify the main pathogenetic link of combined pathology, and therefore, to affect it, preventing progression of diseases. One of these links, often is not taken into account in practice, is the inferiority of mesenchymal tissue, or connective tissue dysplasia.

The following extract from the case history, in our opinion, serves as an illustration of this thesis.

17-year-old adolescent

Main diagnosis: (ICD 10: N13.7) reflux nephropathy. Bilateral vesicoureteral reflux (VUR) grade 2 in anamnesis. Endoscopic correction (EC) of ureterovesical anastomosis (UVA) repeatedly (2 g 9 months and 3 g 11 months); chronic kidney disease (CKD) G1A1. Secondary chronic pyelonephritis, remission period.

Associated diagnoses: primary exogenous constitutional obesity; allergic rhinitis, persistent course; pollinosis; type 2 hiatal hernia; reflux esophagitis.

Family anamnesis: mother has type 2 diabetes mellitus, hypertension, obesity, urolithiasis, allergy, pancreatic cancer.

Anamnesis vitae: the boy was born from the 1st pregnancy with the development edema and pyelonephritis; caesarean delivery section was done at 40 weeks. At birth, body weight was 4450 g, length — 55 cm, Apgar score 8/8. Breastfeeding was up to 9 months; excessive weight gain formed from age 12. At the age of 12, allergic bronchitis, allergic rhinitis and pollinosis were diagnosed; at 7 years old, diagnosis: "acute polyradiculoneuritis; lower extremity paraparesis" was done.

Anamnesis morbi: "unmotivated" rises in temperature from 9 months. The first examination by urologist was at 2 years 9 months — bilateral VUR, secondary contracted left kidney; chronic pyelonephritis. Repeated EC UVA at 2 years 9 months and at 3 years 11 months.

State of the urinary system: computed tomography (CT) of the abdominal organs (14 years): left kidney (RS) — 3,1×4,8×7,8 cm; 17 years old: 0,92×0,38 cm, pyelectasia, dilatation of the ureter. Right kidney (RD) (14 years) — 4,8×6,2×10 cm; 17 years old: 1,28×0,52 cm.

Dynamic renal scintigraphy (14 years): severe disturbances in secretory and excretory functions of RS; renal index 29,1%; RD — moderate; renal index 70,1%; transport of the radiopharmaceutical is slowed down on both sides. The last exacerbation of pyelonephritis occurred at the age of 12.

Increases in blood pressure — from 14 years of age (max. 145/98).

Blood biochemistry test: blood creatinine 82 μmol/l; GFR (Schwartz) 135,2 ml/min/1,73 m^2.

Urine: specific gravity 1,007–1,020; albumin 29,3 mg/l; albuminuria 61,17/24 hours.

State of the digestive system: Ultrasound — signs of hepatomegaly with fatty infiltration, biliary dyskinesia, reactive changes in the liver and pancreas.

Fibrogastroduodenoscopy: type 2 hiatal hernia, grade A reflux esophagitis; HP+ gastritis. Fasting glucose level 5,16 mmol/l; HOMA-IR = 2,97 (normal).

Four systems are involved in the pathological process: the nervous system, organs of the urinary system, digestive system, and immune system (allergosis). The concept of the patient dictates the search for a single link in pathogenesis. We hypothesized that connective tissue dysplasia may be a basis for this comorbidity. Connective tissue dysplasia (CTD) is a genetically determined condition characterized by defects in the fibrous structures and ground substance of connective tissue, leading to impaired of the formation of organs and systems. CTD has a progredient course, which defines the features of the related pathology, as well as the pharmacokinetics and pharmacodynamics of drugs [3].

In a 17-year-old adolescent, 4 systems are involved in the pathology:

- urinary system pathology — VUR, complicated by reflux nephropathy and pyelonephritis;
- digestive system pathology — hiatal hernia and reflux esophagitis;
- signs of CTD of the nervous system — disorders of the autonomic nervous system; dysplastic polyneuropathy — polyradiculoneuritis, lower extremity paraparesis;
- disorders of the immune system — allergic bronchitis, allergic rhinitis, persistent course.

This comorbidity suggests the presence of one cause — failure of mesenchymal tissue, or undifferentiated connective tissue dysplasia (CTD).

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To confirm this assumption, it is necessary to supplement the examination with the following methods: family anamnesis and characteristic complaints; biochemical parameters; morphological diagnostics; dermatoglyphics.

The pedigree often reveals comorbidity in pathology of the heart, kidneys, pathology of the gastrointestinal tract, and excessive joint mobility. The most typical patient complaints are fatigue, weather sensitivity, cardialgia, and dizziness.

Basic laboratory diagnostics include a complete blood count, urinalysis, biochemical parameters of acute phase reactions, protein, fat, carbohydrate metabolism, micro- and macro-elements. It is most promising to study metabolites of connective tissue in blood serum, saliva and gastric juice for biochemical confirmation of CTD. The most important parameters during collagen breakdown in tissues are hydroxyprolines (HYP); the level of free HYP is a marker of collagen degradation; HYP-containing peptide reflects both the processes of collagen synthesis and degradation. Glycosaminoglycans, as well as fractions of sialic acids, fucose, and mannose, can serve as markers of proteoglycan degradation and the state of both collagen and glycoprotein metabolism in CTD.

Morphological diagnostics in pediatric practice involves non-invasive methods. Bone densitometry in CTD reveals a decrease in mineralization in flat and tubular bones. One of the most reliable evidence of the presence of CTD is the identification of changes in tooth enamel from childhood. Enamel prisms are the main structural and functional units of enamel, passing in bundles through its entire thickness radially and slightly curved in the shape of the letter S. Based on the results of a study of the ultrastructure of dental enamel, we can talk about a disturbance of the mineralization and organization of enamel prisms in persons with signs of CTD. This is explained by the insufficient packing density of enamel prisms per unit volume, their chaotic arrangement, and insufficient organized and mineralized matrix [4].

Dermatoglyphics, as a method of human genetic research, contributes to the diagnosis of CTD. Sections of dermatoglyphics: fingerprinting — the study of patterns on the pads of the fingers, and plantoscopy — the study of dermatoglyphics of the plantar surface of the foot. With undifferentiated CTD, the development of pachydermodactyly (from the Greek *pachy* — thick, dense, hard) is possible. Morphological changes in pachydermodactyly are characterized by hyperkeratosis, acanthosis, increased dermis thickness, expressed in varying degrees by fibroblast proliferation, and sometimes mucin deposits. An immunohistochemical study of the dermis reveals an increased amounts of types III and V collagen [5].

Indications for genetic counseling confirming/rejecting CTD:

- established or suspected hereditary disease in the family;
- the birth of a child with a congenital malformation;
- physical development delay or mental retardation in a child;
- recurrent spontaneous abortions, miscarriages, stillbirths;
- pathology detection during screening programs;
- consanguineous marriages;
- exposure to known or possible teratogens during the first 3 months of pregnancy;
- unfavorable pregnancy.

The principles for treating CTD are presented in detail in the National Guidelines [3]. The special importance of informing the patient and his parents (legal representatives) about the concept of "CTD", as well as the need for an individual approach to each clinical case, is emphasized. General recommendations include advice on physical activity and a balanced diet. It is necessary to choose the right type of physical activity, adequate load and pace of training. In addition to morning exercises, it is necessary to perform aerobic exercise 3 times a week for 40–60 minutes (swimming, walking or moderate running on a treadmill, cycling/stationary biking, skiing in winter, badminton, bowling, table tennis). Such types of training loads as choreography, team sports with a high probability of injury, weightlifting, as well as chess and piano playing are not recommended due to prolonged static loads (sitting position). High-protein foods containing significant amounts of chondroitin sulfates are recommended. All patients with CTD are recommended to consume products fortified with substances involved in connective tissue metabolism — vitamins C, E, B6, D, P and microelements: magnesium, copper, manganese, zinc, calcium, selenium, sulfur.

CONCLUSION

Comorbidity in pediatrics is an insufficiently studied phenomenon. A patient diagnosed with two or more types of pathology should be observed by a team of specialists. In this case, it is necessary to find a common link in pathogenesis. In addition to mesenchymal deficiency, conditions such as endothelial dysfunction, undiagnosed poly-deficiency conditions, and genetic abnormali-

ties are possible. It is planned to develop reliable markers for different types of comorbidity in children.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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