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Стаття надійшла 24.08.2020 р.

DOI 10.26724/2079-8334-2021-3-77-137-142
UDC 616.988.55-053.2-36.002-091.8

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CLINICAL-MORPHOLOGICAL FEATURES OF LIVER CHANGES IN CHILDREN WITH MONO- AND MIXED-ASSOCIATED TYPES OF INFECTIOUS MONONUCLEOSIS

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This article considers the clinical features of course of mono- and mixed-associated infectious mononucleosis in 60 patients with and without liver lesions. It was established that symptoms duration of infectious mononucleosis in patients with mixed-associated type were significant longer compared to mono-variant. The similar significant deviation was detected in laboratory tests in patients with mixed-associated infectious mononucleosis. The tendency to detection morphometric and echoacoustic changes of the liver, using ultrasound technique, was noted in the same group of patients. Were established clinical independent predictors of liver lesions in patients with infectious mononucleosis as: concomitant anemia, female sex, age > 10 years. During scientific studies morphological changes of the liver in patient with infectious mononucleosis were described with typical signs such as: moderate lymphohistiocytic infiltration, hepatocyte protein dystrophy, moderate manifestations of coagulation necrosis of centrilobular hepatocytes, endothelial desquamation and moderate manifestations of intraductal cholestasis. The presence of EBV-virus was confirmed by immunohistochemistry essay.

Keywords: infectious mononucleosis, children, hepatitis, herpes infection.

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КЛІНІКО-МОРФОЛОГІЧНІ ОСОБЛИВОСТІ ЗМІН ПЕЧІНКИ У ДІТЕЙ ІЗ МОНО- ТА МІКСТ-АСОЦІЙОВАНИМ ВАРІАНТОМ ІНФЕКЦІЙНОГО МОНОНУКЛЕОЗУ

У цій статті наведено клінічні особливості перебігу моно- та мікст-асоційованого варіанту інфекційного мононуклеозу у 60 пацієнтів з та без ураження печінки. Встановлено, що тривалість симптомів інфекційного мононуклеозу у пацієнтів зі мікст-асоційованим типом була значно вищою порівняно з моно-варіантом захворювання. Подібне значне відхилення було виявлено в лабораторних дослідженнях у пацієнтів з мікст-асоційованим інфекційним мононуклеозом. Тенденція до виявлення морфометричних та ехоакустичних змін печінки за допомогою ультразвукового дослідження відзначена у тій ж групі пацієнтів. Були встановлені незалежні клінічні предиктори ураження печінки у пацієнтів з інфекційним мононуклеозом такі, як: супутня анемія, жіноча стать, вік > 10 років. У процесі наукового дослідження морфологічні зміни печінки у пацієнтів з інфекційним мононуклеозом були описаними з типовими ознаками, такими як: помірна лімфогістіоцитарна інфільтрація, білкова дистрофія гепатоцитів, помірні прояви коагуляційного некрозу центрлобулярних гепатоцитів, десквамація ендотелію та помірні прояви внутрішньопотокового холестазу. Наявність EBV-вірусу у біоптатах було підтверджено імуногістохімічним дослідженням.

Ключові слова: інфекційний мононуклеоз, діти, гепатит, герпетична інфекція.

The work is a fragment of the research project “The course of viral and bacterial infections in children depending on genetic, immunological, metabolic and morphological factors”, state registration No. 0120U100609.

According to the WHO, in the structure of infectious pathology, mortality from diseases caused by herpesviruses took second place after influenza [7]. Among the diseases, which caused by herpes viruses, infection of the immune system such infectious mononucleosis (IM) has been studied by scientists nowadays.

The Epstein-Barr virus (EBV) infects from 16 up to 800 people per 100,000 population each year The incidence of IM is constantly growing both around the world, also in Ukraine: over the last 10 years it has more than doubled [3]. It has been established that the EBV-virus is associated with oncological, mainly lymphoproliferative and autoimmune diseases. Until recently, the development of IM was associated exclusively with EBV-virus. Nowadays, it has become clear that IM can be caused by other pathogens, mainly by members of herpesviruses family (CMV, HHV-6, HHV-7). Carriers of these viruses are more than 90 % of the world's population, however, the acute form of the disease is more common in childhood [5, 9]. These

pathogens are characterized by multiple transmission pathways, general variability, ubiquity, high contagiousness, latency, low immunogenicity, tropism to the skin and mucous membranes, cells of the nervous and immune systems, viscerotropy, association with the development of chronic recurrent inflammatory processes and oncogenicity. In case of EBV-infection, usually liver lesions manifest as predominant cytolysis syndrome, non-jaundiced forms with long-term preservation of liver dysfunction [6]. Thus, in the current problem of IM remains a fairly large list of issues that need to be studied, in case liver lesions [15].

According to the literature, the largest percentage of cases of viral hepatitis in children of the first year of life is caused by CMV. The main clinical signs are the development of prolonged jaundice, cholestasis, early onset of the disease with increasing levels of transaminases. In 20 % of these patients, hepatomegaly can be detected for a long time, with a slow regression of biochemical parameters [10]. Severe liver damage with the development of hepatitis is associated with infection in the liver of local T- and NK-lymphocytes, which initiate cell-mediated cytolysis of hepatocytes [10]. Some researchers point to the possibility of development of liver fibrosis and cirrhosis, acalculous cholecystitis, inflammation of endothelial cells, massive liver necrosis [1, 5]. Should be noted than, with age, the risk of liver lesions in the background of mixed-associated type of IM in patients increases.

Immunological mechanisms play an important role in the pathogenesis of hepatitis in case of IM. The great importance is the change in the number of immunocompetent cells, T-helpers, and liver damage by autoimmune mechanism is not a key, as evidenced by the high level of T-suppressors [2]. According to the literature, morphologically, such patients could have portal, periportal and sinusoidal lymphocytic infiltration, proliferation of Kupffer cells and tubules of the biliary tract. All this occurs against the background of both isolated and draining foci of necrosis and the formation of granulomas.

The analysis of the role of TLR-4 gene polymorphism is becoming more widespread not only in patients with chronic viral hepatitis B and C, but also in other clinical conditions, including IM [4, 11]. The study of features of liver damage in pediatric patients with mono- and mixed-associated types of IM is relevant.

The purpose of the study was to evaluate the clinical and morphological changes of the liver and the features of its damaging in children with infectious mononucleosis by clarifying the role of mono- and mixed-associations of herpes viruses in the relationship with independent clinical and diagnostic predictors.

Materials and methods. The main direction of the study was to determine the clinical features of liver damaging in children with mono- and mixed-associated types of IM. The research methodology includes detailed verification of clinical changes of the liver, including the results of laboratory tests (CBC, etc.), biochemical parameters indicating liver damage (ALT, AST, indicators of total, direct and indirect bilirubin) and instrumental data research methods (ultrasound examination of the abdomen).

In the process of scientific research on the basis of Communal Nonprofit Enterprise “Vinnitsya Regional Clinical Childrens’s Infectious Diseases Hospital, Vinnitsya Regional Council” as a result of a retrospective review were analyzed 60 patients with mono-variant IM (EBV) and mixed-associated type of IM (EBV, CMV, HHV-6, HHV-7), who were registered at dispensaries in treatment facilities, including 53 % (n=32) of cases with diagnosed hepatitis on the background of IM, and 47 % (n=28) of cases – IM without signs of hepatitis.

Among all examined patients with a mono-variant of IM in 34 % (n=10) of cases clinical signs of hepatitis were detected, in 66 % (n=20) of cases – there were no signs of liver injury. Compared to mono-variant of IM, in patients with a mixed-associated type of IM in 73 % (n=22) of cases hepatitis was detected, while in 27 % (n=8) of patients – hepatitis had not been detected.

It should be noted that further research and statistical analysis were performed with a group of children with hepatitis which had developed on the background of mono- (n=10) and mixed-associated type of IM (n=22).

The mean age of the examined children with mono-variant of IM was 6.3 ± 1.05 years, and mixed-associated IM – 11.4 ± 1.2 years ($p < 0.01$).

The distribution of children by sex in the group with mono-variant IM was as follows: male sex representatives – 7, female – 3, respectively, in the group with mixed associated type of IM – boys were 10, girls – 12 patients.

The relative risk of hepatitis in patients with mixed-associated IM is 2.2 times higher than in patients with mono-variant of IM (RR=2.2; CI 1.2691 3.8138; $p=0.0050$).

Among patients with mixed-associated type of IM in 75 % of patients (n=16) by ELISA and PCR were determined association of EBV and CMV, in 13 % (n=3) – the etiological factor of IM was the association of EBV and HHV-6, in 8 % (n=2) – association of EBV, CMV, HHV-6, HHV-7, in 4 % (n=1) – association of CMV and HHV-6.

The pathohistological material of 8 deceased patients with liver changes due to cytopathogenic and lymphotropic action of herpes viruses in the period from 2015 to 2020 was analyzed on the basis of the pathological anatomical bureau (fixation in 10 % buffered formalin solution, degreasing, waxing with filling into blocks, microtomy with obtaining 3-4 μm thick sections and staining with hematoxylin-eosin),

immunohistochemical study was performed in the Pathology Department of the Center for Reconstructive and Renewable Medicine (University Clinic) of Odessa National Medical University, was used monoclonal antibodies pp56 ("Abcam", clone 2 + 6), Epstein-Barr virus ("Abcam", clone E1-2.5), herpes virus type I ("Cell Marque", clone 10A3), polyclonal antibodies to herpes virus type II ("Cell Marque", clone 10A3) and termo visualization system with internal and external quality controls. The expression of viral particles was determined by a semi-quantitative method: +++ – expressive, ++ – moderate, + – weak, (-) and (+/-) – negative and insignificant expression. A digital camera (Leica CTR 5000) was used to visualize the images.

Clinically and anamnestically, all other factors that can lead to liver injury, including viral hepatitis, exacerbation of chronic nonspecific inflammatory processes, hereditary and mental diseases, as well as alcohol abuse, hepatotoxic and myelotoxic drugs intake were excluded in these patients. The diagnosis of infectious mononucleosis was formulated according to the ICD-10 classification and was confirmed by ELISA and PCR testing.

Qualitative and quantitative analysis of the results were evaluated during the study data collection. Statistical analysis of the study materials was performed using methods of parametric statistics, reliability assessment using of a pair of Student's t-test, estimation of relative risk (RR) and estimation of degree of probability (p) using the software "Statistica 10.0". The results are presented as mean (M) and mean error (m) for quantitative values. The significance of the difference was determined at the normal distribution by Student's t-test. Differences at $p < 0.05$ are considered reliable. Additionally, a correlation-regression analysis was performed with the obtained results in order to determine the direction and strength of the relationship between estimated values.

The research was performed according to the obligation of Helsinki declaration.

Results of the study and their discussion. It should be noted that in patients with mono- and mixed-associated IM premorbid background was mainly burdened by concomitant anemia, a history of infectious diseases in anamnesis (measles, chickenpox and others), frequent episodes of upper respiratory viral infections (URVI), somatic diseases of the hepatobiliary zone (chronic gastritis and duodenitis, chronic pancreatitis, etc.).

Having clarified the features of age, sex distribution, the presence of concomitant pathology of patients with mono- and mixed associated type IM, the features of the clinical course of IM in comparison groups were analyzed. It was established that in the group of children with mixed-associated type of IM the duration of difficult in nasal breathing (5.3 ± 0.36 days) was longer than in the group with mono-variant course of IM (4.2 ± 0.4 days) ($p < 0.05$). This trend is determined for the symptom such as fever, so the duration of fever in patients with mixed- IM was 6.4 ± 0.3 days, which was significantly longer compared with patients with mono-variant of IM (4.4 ± 0.6 days) ($p < 0.05$).

It should be noted that the signs of tonsillitis in the group of patients with mixed-associated type of IM (10.6 ± 0.7 days) lasted longer than in the group of patients with mono-variant of IM (7.4 ± 0.9 days) ($p < 0.05$). The presence of lymphadenopathy was estimated longer in patients with mixed-associated type of IM (13.7 ± 0.5 days), compared with mono-variant of IM (10.8 ± 0.6 days) ($p < 0.05$).

Regarding the symptoms of hepatobiliary zone lesions (loss of appetite, discomfort in right hypochondrium, enlargement of liver and spleen), there were no clinically significant difference between their manifestations in comparison groups.

Patients with mixed-associated IM were hospitalized significantly longer (7.2 ± 0.6 bed-days) than with mono-variant of IM (5.2 ± 0.4 bed-days) ($p < 0.05$).

In addition, the duration of the disease in the group with mixed-associated type of IM was significantly higher compared with the group with mono-variant of IM, and was 14.8 ± 0.9 days, compared to 10.4 ± 1.2 days in the group with mono-variant of IM ($p < 0.05$).

Having clarified the features of clinical symptoms of mono- and mixed-associated IM, we analyzed the laboratory features in the comparison groups (table 1). It was estimated that deviation of laboratory tests (total bilirubin level, ALT, AST, platelet count, level of atypical mononuclear cells) was clinically significant presented in patients with mixed-associated type of IM compared to mono-variant of IM.

Table 1

Features of laboratory parameters in patients with mono- and mixed-associated types of IM (M \pm m)

| Criterion | Mono-variant of IM (n=10) | Mixed- associated type of IM (n=22) |
|---|---------------------------|-------------------------------------|
| Total bilirubin ($\mu\text{mol/l}$) | 11.8 ± 1.4 | $17.9 \pm 1.8^*$ |
| ALT (IU/l) | 48.42 ± 6.5 | $76.58 \pm 5.2^{**}$ |
| AST (IU/l) | 37.18 ± 3.4 | $54.29 \pm 4.2^{**}$ |
| Platelet count ($\times 10^9/\text{l}$) | $154.9 \pm 6.8^{**}$ | 129.5 ± 4.2 |
| The level of atypical mononuclear cells (%) | 16.2 ± 0.8 | $19.8 \pm 1.2^*$ |

Note: * – there is clinically significant difference between comparison groups with $p < 0.05$ taking into account the paired Student's t-test. ** – there is clinically significant difference between comparison groups with $p < 0.01$ taking into account the paired Student's t-test.

Having clarified the features of clinical symptoms and laboratory data, we aimed to investigate the peculiarities of liver damage using ultrasound technique (table 2). After analysis of morphometric and echoacoustic parameters of the liver and spleen using ultrasound technique, it was established that the size of the right lobe of the liver, spleen size, strengthening of the vascular component were clinically significant presented in patients with mixed-associated type of MI compared with mono-variant IM.

□□b□□2

Morphometric and echoacoustic parameters of abdominal organs in patients with mono- and mixed-associated IM and hepatitis according to the data of ultrasound of the abdomen (M±m)

| Criterion | Mono-variant of IM (n=10) | Mixed-associated type of IM (n=22) |
|---|---------------------------|------------------------------------|
| Abdomen ultrasound data (morphometric parameters) | | |
| The size of the right lobe of the liver (in times, comparing to the age norm) | 1.08±0.04 | 1.21±0.03* |
| The size of the caudate lobe of the liver (in times, comparing to the age norm) | 1.06±0.05 | 1.14±0.03 |
| Spleen size (in times, comparing to age norm) | 1.12±0.05 | 1.24±0.03* |
| Abdomen ultrasound data (echoacoustic indicators) | | |
| Change in echogenicity of the liver | 8 (80 %) | 17 (77 %) |
| Strengthening of the vascular component | 3 (30 %) | 16 (72 %)* |

Note: * – there is clinically significant difference between comparison groups with $p < 0.05$ taking into account the paired Student's t-test.

A correlation analysis had shown that in patients with IM, the occurrence of hepatitis significantly correlates with the level of concomitant anemia ($r=0.561$; $p < 0.05$), frequent URVI in the anamnesis ($r=0.46$; $p < 0.05$), infectious diseases in the anamnesis ($r=0.54$; $p < 0.05$), somatic diseases in anamnesis (hepatobiliary region lesions) ($r=0.51$; $p < 0.05$), as well as female sex ($r=0.42$; $p < 0.05$), age > 10 years ($r=0.44$; $p < 0.05$).

In a multivariate analysis, by forming a logistic regression model, it was estimated that the independent predictors were: presence of concomitant anemia ($\beta=0.38$; $p=0.005$), female gender ($\beta=-0.21$; $p=0.009$) and age > 10 years ($\beta=0.34$; $p=0.000026$). The factorial logistics model was reliable with a coefficient of determination $R^2 = 50\%$.

In necropsies of the liver, it was found that the degree of injury varied from moderate changes in the liver parenchyma and stroma to pronounced irreversible changes. All cases were immunohistochemically confirmed by the presence of Epstein-Barr virus in the material. Signs of protein and lipid dystrophy of hepatocytes of various degrees and stroma edema prevailed. Documented in 3 cases of violation of parenchymal-stromal relations, moderate exudative processes, moderate signs of inflammation (fig. 1).

In 3 cases there were sharply expressed alternative changes, up to coagulation necrosis of a part of centrolobular hepatocytes, karyopyknosis and karyolysis, deep disintegration of cytoplasm, detection of lipofuscin in a part of the saved cells are documented. The foci of necrosis, located mainly centrilobular, tended to merge (fig. 2).

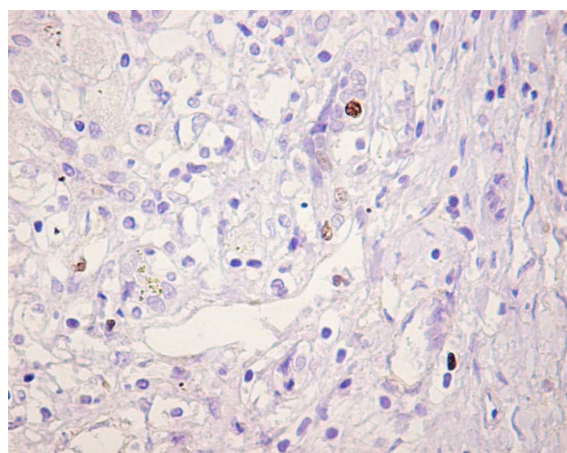


Fig. 1. Patient D., 16 years old. Moderate lymphohistiocytic infiltration and a positive immunohistochemical response to Epstein-Barr virus, x400.

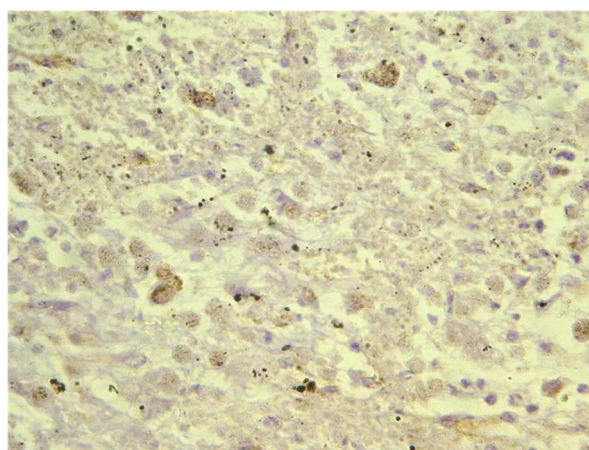


Fig. 2. Patient G., 17 years old. Centrolobular necrosis of hepatocytes and weak inflammatory infiltration of the portal tract, positive immunohistochemical reaction to Epstein-Barr virus, x200.

In two cases, the morphological changes in the liver were less acute, dominated by granular and hyaline-droplet hepatocyte dystrophy. Inflammatory infiltration was concentrated mainly in the portal tracts, was lymphoid-histiocytic in nature with an admixture of macrophages, plasma cells and single neutrophilic leukocytes.

Also, in these cases there was moderate fibrosis of the portal tracts, damage to the small bile ducts with swelling and desquamation of the endothelium, mild intraductal cholestasis. In all cases, indistinct circulatory disorders with plethora, stasis in the vessels of the microcirculatory tract, sludge were detected.

Having analyzed obtained results, it seemed that clinical and laboratory peculiarities of the course of IM with liver injury in pediatric patients has the similar tendency with obtained data of Ukrainian and foreign authors [3, 14]. Instrumental deviations of liver injury in pediatric patients shows that simultaneous infectious pathogens lead to development of severe lesion of the liver [8]. Also, it was estimated that independent clinical predictors of development of liver lesions in pediatric patient with typical course of IM are the same as in foreign authors [13]. Having analyzed, morphological changes of the liver in patients with IM, was established that obtained results are similar to the collected data of colleagues abroad [12]. Should be noted, that received results could be used by pediatrics and general medicine specialists to predict liver lesions in patients with mono- and mixed-associated type of IM.

Conclusions

1. Typical symptoms for mono- and mixed-associated IM are: fever, nasal breathing difficulties, tonsillitis, lymphadenopathy. It was estimated that for patients with mixed-associated IM, the duration of these symptoms was significantly higher than in patients with mono-variant of IM ($p < 0.05$). However, patients with mixed-associated type of IM were hospitalized significantly longer than patients with mono-type of IM ($p < 0.05$).

2. In patients with mixed-associated type of IM, levels of total bilirubin, ALT, AST, platelet count, level of atypical mononuclear cells were significantly deviated compared with patients with mono-type of MI ($p < 0.05$).

3. It was performed that morphological parameter such as the size of the right lobe of the liver and spleen size, echo-pattern (strengthening of the vascular component) were clinically significant highly presented in patients with mixed-associated type of MI compared with mono-variant IM ($p < 0.05$).

4. In multivariate analysis, by forming a logistic regression model, it was noted that independent predictors are: presence of concomitant anemia ($\beta = 0.38$; $p = 0.005$), female sex ($\beta = -0.21$; $p = 0.009$) and age > 10 years ($\beta = 0.34$; $p = 0.000026$).

5. The relative risk of hepatitis development in patients with mixed-associated type of IM is 2.2 times higher than in patients with mono-type of IM (RR=2.2; CI 1.2691 3.8138; $p = 0.0050$).

6. Typical changes of the liver during pathomorphological investigation in patients with IM were: moderate lymphohistiocytic infiltration, hepatocyte protein dystrophy, moderate manifestations of coagulation necrosis of centrilobular hepatocytes, endothelial desquamation and moderate manifestations of intraductal cholestasis.

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Стаття надійшла 30.08.2020 р.

DOI 10.26724/2079-8334-2021-3-77-142-147

UDC 616.728.2-053.2

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STUDY OF THE STRESS-DEFORMED STATE OF THE HIP JOINT MODEL IN CHILDREN UNDER THE CONDITIONS OF DYSPLASIA AND CONSERVATIVE TREATMENT

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In this work, a comparative study of the stress-strain state of the elements of the hip joint in children in normal and in the case of its dysplastic changes in the application of the technique of "trampling" used for conservative treatment of hip dysplasia. To solve this goal, several mathematical models of the child's hip joint were built using the finite element method. In the process of constructing the calculation model, the geometric model of the pelvis-thigh was taken as a basis, which is based on the method of creating a model of geometric sections obtained from tomographic images. As a result of the conducted mathematical research significant changes in the nature of the stress-strain state in normal and dysplastic hip joint using the technique of "trampling" in comparison with previously obtained data for single-support standing, which, in our opinion, may be one of the significant factors joint in the process of conservative treatment. The obtained data should contribute to the definition and optimization of methods of additional mechanical stimulation of the components of the hip joint for its normal development during treatment.

Key words: hip joint, dysplasia, child, biomechanics, acetabulum.

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ДОСЛІДЖЕННЯ НАПРУЖЕНО-ДЕФОРМОВАНОГО СТАНУ МОДЕЛІ КУЛЬШОВОГО СУГЛОБА У ДІТЕЙ В УМОВАХ ДИСПЛАЗІЇ ТА КОНСЕРВАТИВНОГО ЛІКУВАННЯ

В даній роботі проведено порівняльне дослідження напружено-деформованого стану елементів кульшового суглоба у дітей в нормі та у випадку його диспластичних змін в умовах застосування методики «топтання», що застосовується для консервативного лікування дисплазії кульшових суглобів. Для вирішення поставленої мети були побудовані декілька математичних моделей дитячого кульшового суглобу за допомогою методу скінчених елементів. У процесі побудови розрахункової моделі за основу була взята геометрична модель таз-стегно, в основу якої покладено методику створення моделі по геометричних перетинах, отриманих з томографічних знімків. В результаті проведеного математичного дослідження встановлено значні зміни характеру напружено-деформованого стану в нормальному та диспластичному кульшовому суглобі при застосуванні методики «топтання» в порівнянні з раніше отриманими даними для одноопорного стояння, що, на нашу думку, може бути одним із суттєвих факторів дорозвитку диспластичного кульшового суглобу в процесі консервативного лікування. Отримані дані мають сприяти визначенню та оптимізації методів додаткової механічної стимуляції компонентів кульшового суглоба для його нормального дорозвитку в процесі лікування.

Ключові слова: кульшовий суглоб, дисплазія, дитина, біомеханіка, кульшова западина.

The work is a fragment of the research project "Functional treatment of shoulder fractures", state registration No. 0117U4682.

This work is a logical continuation of many theoretical and experimental-biomechanical studies, which show that bone tissue is a mobile and plastic material, and in particular, changes in mechanical loads affect the bone structure by changing its mass and architecture. Thus, the law of J. Wolf formulated in the 19th century states that the bone of a healthy person adapts to the constant periodic loads to which it is exposed. That is, if the load on any bone increases, the bone is rebuilt in such a way as to better withstand the load [5, 8, 10].

According to previous studies, bone growth and/or bone remodeling is stimulated by local cyclic mechanical elastic action (deformation) on the bone. Reconstruction of bone in accordance with the load is carried out by mechanotransduction – the process by which forces and other mechanical signals are converted into cellular signals. It is proved that the effects of cellular reorganization of bone tissue depend on the duration, amplitude and strength of the load, and also the influence of cyclic loads on the stimulation of bone formation was revealed [6, 8].