показниками здорових осіб була достовірно вищою у хворих на ревматоїдний артрит в обох фазах хронічної ЕБВ-інфекції, а в пацієнтів з реактивний артритом - тільки в активній фазі цієї інфекції. Експресія цього рецептору на лімфоцитах виявилась достовірно вищою у хворих на ревматоїдний артрит порівняно із хворими на реактивний артрит саме в активній фазі хронічної ЕБВ інфекції.

Ключові слова: реактивний артрит, ревматоїдний артрит, хронічна Епштейна-Барр вірусна інфекція, TLR9.

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показателями здоровых лиц была достоверно выше у больных ревматоидным артритом в обеих фазах хронической ЭБВ-инфекции, а у пациентов с реактивным артритом - только в активной фазе этой инфекции. Экспрессия этого рецептора на лимфоцитах оказалась достоверно выше у больных ревматоидным артритом по сравнению с больными реактивным артритом именно в активной фазе хронической ЭБВ инфекции.

Ключевые слова: реактивный артрит, ревматоидный артрит, хроническая Эпштейна-Барр вирусная инфекция, TLR9.

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MEASLES PNEUMONIA IN CHILDREN: CLINICAL AND MORPHOLOGICAL FEATURES OF THE COURSE

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The article presents the results of a retrospective analysis of 96 patients' histories with measles established, with a detailed course study and the anamnestic data analysis. The measles infection course was accompanied with signs of the intoxication syndrome, the classic catarrhal triad manifestation (coughing, rhinorrhea and conjunctivitis), and the exanthema syndrome. Most of the diseased children are not vaccinated against measles. The patients had a complicated disease course with manifested symptoms of measles pneumonia, as the most common complication in this pathology. Morphological and histological changes of the lungs in children with severe mesles course were characterized by abundant infiltration of both the interalveolar septa and alveolar lumens by polymorphocellular infiltrate, consisting of neutrophilic leukocytes, eosinophils, lympho-histiocytes with numerous parietal hyaline masses (hyaline membranes). There was a giant-cell metaplasia of the alveolar epithelium.

Key words: measles in children, pneumonia, pathomorphological changes, histological examination.

The work is a fragment of the research project "Early diagnosis of dysplastic, metaplastic and neoplastic changes in the pathology of the gastrointestinal tract, respiratory, urogenital and neuroendocrine system", state registration No. 0117U000001.

At the present stage, measles remains an extremely important problem of today. Both in the world and in Ukraine, every five to six years an increase in the measles incidence is observed. According to the European Regional Bureau of the World Health Organization (WHO), since 2017, over 22,300 measles cases have been reported in different countries of Europe. In 8 countries of the European Region, 57 people died from measles during the first half of 2018 [2].

At the same time, Ukraine occupies a leading position among the countries of the said region. In the period from 1 January to 31 August 2018, 29 465 measles cases were reported in Ukraine, with fatal cases (13 deaths) [2].

Measles is a very threatening and contagious infection. It is known that the risk of this infection lies in the development of serious complications, such as pneumonia, otitis, encephalitis, renal toxicity, polyneuritis, etc. [4, 5]. They are caused directly by the action of the virus itself [6]. Since the measles virus causes cells dystrophy in all mucous membranes, particularly in the respiratory tract, and due to its effect on monocytes, there is an increased production of interleukins, tumor necrosis factor, histocompatibility molecules, and the presentation of antigens to T-lymphocytes is inhibited, these factors cause immunosupression, reduce cellular immunity [7]. T-cell immunodeficiency is particularly pronounced, persisting for 25-30 days after the disease (post-measles anergy) [4]. Against this background, all conditions are created for the development of secondary bacterial complications [7].

In the Vinnytsya region, for the period from January 2018 to February 2019, 4805 persons were diagnosed with measles, including 2210 children. It should be noted that children with the most severe measles course were treated at the Vinnytsya Regional Children's Clinical Infectious Diseases Hospital (VOCDIL).

Within the period from January 2018 to April 2019, 781 patients with measles were treated in hospital. Among all cases of the complicated measles course, measles pneumonia was most commonly reported. In one of the complicated measles cases, the disease had fatal outcome. The death was due to the development of pneumonia against the background of congenital lung pathology.

The purpose of the study was to find out clinical and morphological features of the pneumonia course in children with measles.

Materials and methods. According to the purpose of the study, 96 children between the ages of 1 month and 17 years (mean age 8.6±1.2 years) who were hospitalized in VOCDIL with measles diagnosed during 2018-2019 were monitored. Among 96 patients, boys - 50 children (52%) - were more likely to suffer from measles, the number of girls was 46 (48%) respectively. The patients were divided into two subgroups: 1) 77 children diagnosed with measles without pneumonia (mean age 7.79±4.83); 2) 19 patients with signs of measles pneumonia (mean age - 5.75±3.79).

Determining the severity of the disease was performed by analyzing clinical and medical records and laboratory parameters. At the same time, epidemiological, general clinical, instrumental (ultrasound examination of the abdominal organs, radiological examination of the thoracic organs) research methods were applied. To verify the measles infection, an enzyme immunoassay method was used to detect M. antimeasles immunoglobulins in the patients' blood serum. The severity of pneumonia was assessed by the pneumonia severity scale in children, based on the pneumonia severity index in children (Pneumonia Severity Index).

The disease clinical manifestations' severity was determined, such as age, presence of concomitant diseases, impaired consciousness, labored breathing, cyanosis, chest pain, toxic encephalopathy, body temperature <36ºC, tachycardia; and laboratory-functional parameters such as: leukocytosis, leukopenia, anemia, pH <7.35, residual nitrogen> 11 mmol/l, hematocrit <30%, SaO2 <90%, cardiovascular disorders, radiographic multilobar infiltration, infectious-toxic shock, pleural exudate, destruction.

In this case, a score was developed for each identified symptom. According to the definition of some of the above symptoms, it is possible to establish the severity of pneumonia, namely: if less than 50 are registered when calculating points, this condition indicates the first severity degree of the disease, with the risk of mortality being 0.1%; in the case when the sum of points ranges from 51 to 70 points, the second severity degree is established when the risk of lethality makes 0,6%. With the third severity degree (71 - 90 points) mortality risk makes 2,8%, data on 91 to 130 points testify to the fourth severity degree when mortality risk makes 8,2%. The worst course of the disease is the fifth severity degree (> 130 points), which indicates a high risk of mortality - 29,2% [3]. Given that the main complication in children with measles was pneumonia, the performed scientific research demonstrates the study of this particular contingent of patients.

Statistical processing of the results was performed using STATISTICA 10.0 software for Windows 10 using descriptive statistics methods. Data calculation was performed by processing absolute values taking into account intensive and extensive indices using standard statistic research methods. The results are presented as mean (M) and mean error (m) for quantitative values. Assessment of the difference reliability between the parametric values obtained in the process of scientific research was carried out according to the Student's t-test. The Relative Risk, confidence interval (CI), and its reliability were calculated using the Fisher method in the "2×2" conjugate tables.

Results of the study and their discussion. In the course of our work, it was found that in 59 children (62%) the measles diagnosis was confirmed by laboratory methods, and in 37 patients (38%) it was based on clinical data.

All patients had a typical form of measles. In 92 (96%) children, the disease course was of moderate severity, whereas the severe form of the disease was only diagnosed in 4 patients. Among all the patients, 44 children (46%) had a burdened premorbid background. Complications of the perinatal period were identified in 33 (34%) patients. During the collection of epidemiological histories, it was found that 58 (56%) children had previous contact with measles patients. The overwhelming number of patients –78 patients (81%) - were unvaccinated. In 70 patients (73%) measles progressed without complications. Among the 26 patients (27%) who had a complicated measles course - in 19 (20%) patients, pneumonia was diagnosed as the most common complication. Among 19 children diagnosed with pneumonia, 11 children (58%) were aged 3 - 17 years, 6 (31%) patients were aged 6 months. - 3 years and 2 (10%) infants were less than 6 months old. Burdened premorbid background was significantly more common in children of group 2 than among patients in group 1 (p <0.001) (table 1).

In addition, it was determined that patients with burdened premorbid background were by 37.44 times more likely to develop pneumonia against the background of measles infection (SI - 4.73; 296.53; p <0.00001). The features of measles pneumonia clinical symptoms revealed by us are in agreement with the data of literature sources [8, 11], namely: intoxication syndrome was characterized by severe fever in all patients, with the hectic type of temperature curve (39.1 - 40.2ºC), it was reliably more frequently encountered among patients in group 2 (p <0.001), whereas pyretic fever was reliably more frequently reported in patients of group 1 (p <0.01). The average duration of fever in measles diseased children with development of pneumonia was significantly longer than in children without pneumonia (p <0.05) (table 1). The catarrhal period was characterized by clear clinical symptoms and included the presence of a typical

symptoms triad: cough, rhinorrhea, conjunctivitis, which was noted in the vast majority of patients in both groups 1 and 2, with catarrhal symptoms more common in patients of both groups 1 and 2, with catarrhal symptoms being some more frequently reported in patients of group 2 (table 1).The presence of pathognomic measles signs, such as measles enanthema, was more frequently observed in patients of group 2 ($p < 0.01$) than in patients of group 1; as well as the presence of Koplik spots on the mucous membrane of the oral cavity, which was diagnosed more frequently ($p < 0.01$) in patients with measles pneumonia than in those with uncomplicated pneumonia (table 1). The mean duration of catarrhal period in patients of group 1 was significantly less than in patients of group 2 ($p < 0.05$) (table 1). Therefore, it can be concluded that the oral mucosa injuries were more intense in children with measles pneumonia. The data obtained by us coincide with the data of foreign literature [12].

The rash period was characterized by the onset of typical spotty-papular exanthema in children, with a tendency to fuse mainly on the face skin and the upper chest, as evidenced by the literature data [4, 9].

Table 1

Distribution of patients by severity and duration of clinical symptoms

Symptom	Nosological entity			
	Measles without pneumonia n–77		Measles with pneumonia n–19	
	abs.	%	abs.	%
burdened premorbid background	25	32	18	95***
Fever				
subfebrile	6	8	0	0
febrile	64	83	4	21**
hectic	7	9	15	79***
mean temperature in patients, ºC	38.02±0.62		39.6±0.48*	
mean duration of fever, days	4.88±0.92		7.32±0.72*	
measles enanthema	11	14	13	71***
Koplik symptom	6	8	12	61**
cough	63	82	19	100
rhinorrhea	60	79	15	81
conjunctivitis	54	71	14	77
mean duration of catarrhal period, days	3.36±1.13		6.78±1.2*	
mean duration of rash period, days	4.2±0.56		5.52±0.32*	
mean duration of hospital stay, days	5.54±1.28		8.58±0.82*	

Notes: *** statistically reliable data difference between groups at $p<0.001$ (by Student's t-test); ** statistically reliable data difference between groups at $p<0.01$ (by Student's t-test); * statistically reliable data difference between groups at $p<0.05$ (by Student's t-test).

The mean duration of the rash period in patients of group 2 was reliably longer than in patients of group 1 ($p < 0.05$) (table 1).

Given that changes in the lower respiratory tract were mainly determined in children with measles pneumonia, it was found that the development of lung damage in all patients of group 2 was accompanied by frequent painful low-productivity heavy cough, signs of respiratory failure of varying degrees, namely: degree I respiratory failure (RF) was diagnosed in 17 (90%) patients, while degree II RF, as well as degree III RF was diagnosed in 1 case each (5%), respectively. Almost every third child – namely 7 (37%) patients - had sluggishness and retardment of movements, while severe impairment of consciousness was registered in 2 patients (10%): in one child - due to the development of measles encephalitis; in the other - due to swelling of the brain. Cyanotic changes in the skin and in visible mucous membranes as a result of respiratory failure were observed in 3 (16%) patients of group 2. Given the above, it was found that the mean duration of hospital stay for children with measles pneumonia (group 2) was significantly longer than for patients in group 1 ($p < 0.05$) (table 1). Therefore, the presence of such a complication as pneumonia affects the length of the patient's stay in hospital. Physical data in the examination of patients in group 2 were typical of interstitial pneumonia: laboured breathing, which was recorded in all patients in the study group; as well as suppressed breath sounds in a limited site, unstable dry rales, percussion - tympanic sound. Tachycardia was more frequently reported in children of group 2 - 13 (68%) patients than in group 1 patients - in 18% (14 patients) ($p < 0.01$).

In laboratory studies, it was found that in patients of group 2 - 14 (74%) children were reliably more frequently diagnosed with leukopenia (mean leukocyte $2.8\pm1.35 * 10^9$/l) than in patients of group 1 - 7 (9%) patients ($p < 0.001$). Noteworthy is the fact that in all patients of group 2 in the general blood test, the main deviation from the norm in the leukocyte formula study was a large number of stab neutrophiles

(16-25%) with a reduced number of leukocytes, which can be considered as a manifestation of measles anergy. According to foreign researchers, in studying the measles infection, in the presence of the leukocyte formula left shift, leukopenia was rarely reported [1]. Pulse oximetry (SaO_2) was used in the treatment of group 2 patients. The critical level of SaO_2 <90% was determined in 3 (16%) patients, the SaO_2 level in the range of 92-95% was registered in 4 (21%) patients, but in more than half of the patients - 12 (63%) children, the level of arterial blood oxygen saturation remained within the normal range, namely 95-98%.

All patients with pneumonia without exception were subjected to radiography of the thoracic organs. The radiographs showed characteristic signs - the cord-like or reticulated deformation of the lung pattern, as well as a symptom of "ground-glass opacity" [10]. Multilobar infiltration of the lungs was diagnosed in one patient (5%) in the radiograph, severe cardiovascular disorders were detected in the same patient. Assessing the severity of pneumonia by the pneumonia severity scale in children [3], it was determined that the majority of patients in group 2 - 16 (85%) had the III degree of severity with the risk of lethality - 2.8%. The IV degree of severity and lethality risk of 8.2% were observed in 2 (10%) children of group 2, and only in 1 child (5%) of group 2 was diagnosed with the V severity degree of pneumonia, with mortality risk increasing to 29.2% (table 2). Children with the IV and V severity degree were treated in the intensive care unit (ICU).

T□bl□2

Pneumonia severity in children

Severity degree	Number of points	Lethality risk, %
III (n – 16)	77.5±2.5	2.8
IV (n – 2)	115±5	8.2
V (n – 1)	180	29.2

All patients received pathogenetic, detoxification, desensitizing and symptomatic therapy according to treatment protocols. Antibiotic therapy was prescribed in case of a secondary bacterial infection taking into account the empirical sensitivity of the pathogen.

Clinical case of measles infection with a fatal outcome. Patient M., aged 8 months, was hospitalized in the Vinnytsia OCDIL. The final diagnosis is: measles, typical form, rash period, severe course. Bilateral polysegmental overwhelming interstitial pneumonia. Respiratory failure of the 3rd degree. Respiratory distress syndrome of adults. Multiorgan failure (hepatitis, nephritis, carditis). Disseminated intravascular coagulation syndrome (DIC-syndrome) in the hypocoagulation phase. Edema and swelling of the brain. Acute cardiovascular failure, carditis.

It is known that the infant had a burdened premorbid background and had not been vaccinated according to the vaccination schedule. Having analyzed the clinical course of the disease and the data of the pathoanatomical incision, it became clear that the fatal case occurred because the child had congenital lung pathology, namely, connective tissue dysplasia. Therefore, we were interested in the results of pathomorphological and pathohistological changes in lung tissue against a background of measles infection.

During the study, it was found that the airways mucosa was swollen, white and cyanotic. The lungs do not fill the pleural cavities, occupying about 2/3 of them, with numerous vesicles, mostly subpleural, having the diameter of 0.5 to 2.0 cm, with thin transparent walls (fig. 1). The perihilar divisions are cord-like, with the compacted walls of the bronchi projecting above the incision level in the form of "goose feathers". The lungs consistency is nonuniform, indurated, doughy, fleshy.

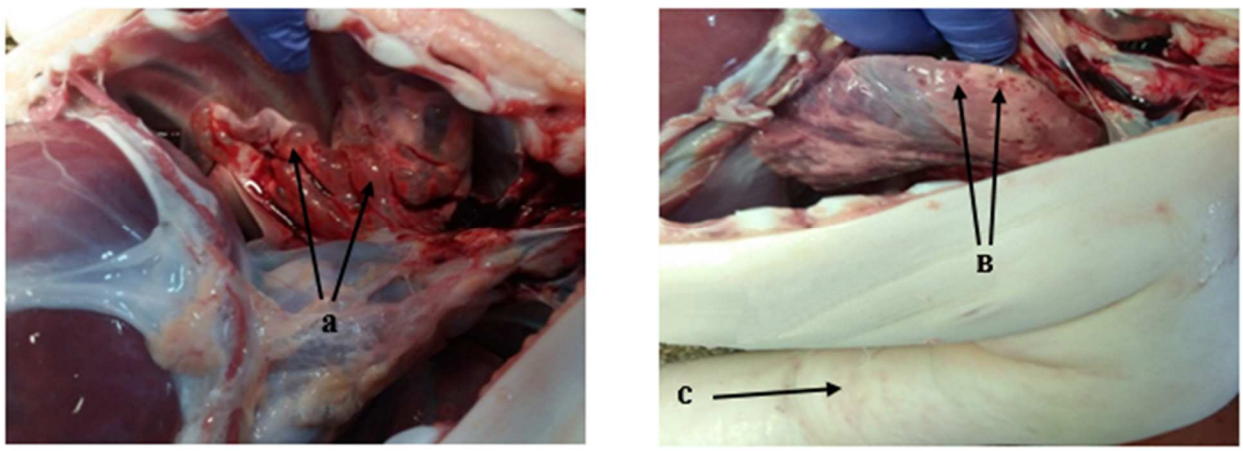

Fig. 1. Blebs located subpleurally in the lungs (a), numerous hemorrhages (b) skin rash (c).

Histological examination of the internal organs showed that the measles virus has particular tropism to respiratory organs' cells. A typical response of the respiratory tract tissues in measles patients was epithelial metaplasia into stratified squamous epithelium with keratinization and spreading from the larynx to terminal bronchioles. The structure of the lungs is impaired due to numerous multifarious cavities, mostly subpleural ones, which are almost unconnected to the bronchial tree and covered both with flattened alveolar and atypical giant cell epithelium; bronchi are polymorphous – their epithelium is metaplastic stratified squamous, vessels are irregularly full-blooded with widespread extravasates, abundant infiltration of both the interalveolar septum and the alveoli lumens with polymorphocellular infiltrate, consisting of neutrophilic leukocytes, eosinophils, lympho-histiocytes, with numerous parietal hyaline masses (hyaline membranes).

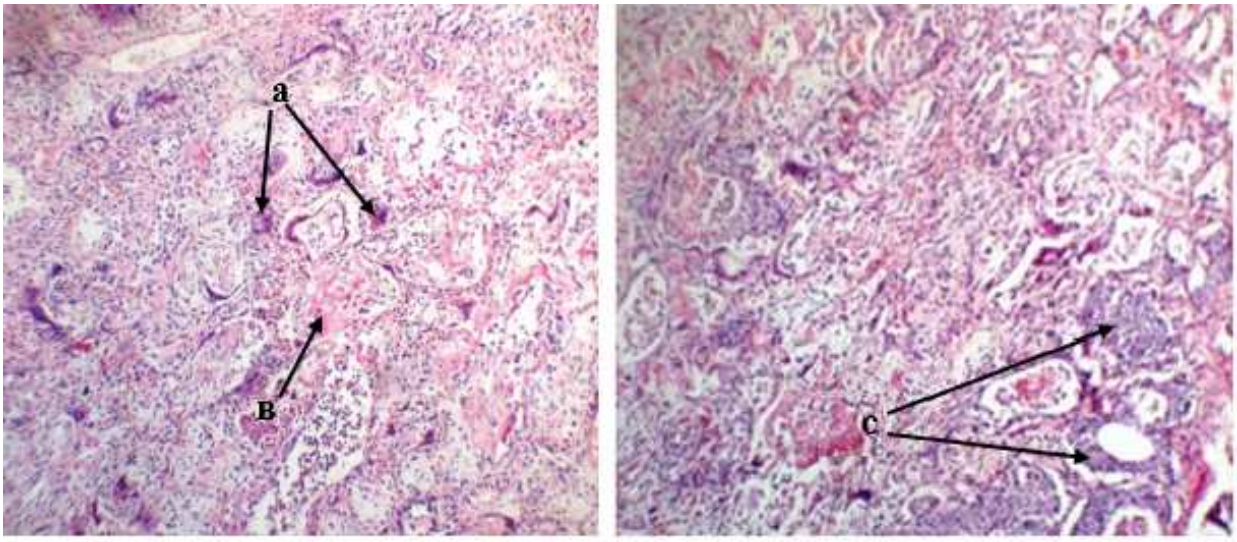

Fig. 2. Interstitial infiltrate of mononuclear and multinucleated cells (a), swelling of the interveolar septa interstitium (b), squamous cell metaplasia (c). Microslide (magnification x100, stain - hematoxylin - eosin).

There is a giant cell metaplasia of the alveolar epithelium (2nd order alveolocytes) (fig. 2). Peribronchial lymphoid tissue is "depleted", mainly represented by immature lymphocytes, without light centers in the lymphoid follicles.

During the analysis of the disease lethal case, certain risk factors for the unfavorable course development were identified, namely, early age of the child, burdened epidemiological history, unsatisfactory vaccinal status, burdened premorbid background, and most important being congenital lung pathology –connective tissue dysplasia.

Thus, having studied clinical and laboratory features of the measles infection course in children, it is established that children of school age are more likely to be diseased (mean age - 8.6±1.2 years). A significant impact on the disease development is produced by unsatisfactory planned immunization. The infection most frequently occurs in a typical form, which has been demonstrated among other foreign researchers [8, 10]; with acute onset and predominance of moderate severity course. The complexity of the comparison is due to the lack of modern work to study the features of the course of measles pneumonia in children. Somewhat close to our study are the scientific works of V. Gnatyuk and T. Pokrovskaya [1] in the clinical field, confirming some of our findings. Most frequently, the complicated course of infection is characterized by damaged lower respiratory tract, i.e. by the development of interstitial measles pneumonia. This complication was more common among children aged 3 to 17 years (mean age - 5.75±3.79), almost all patients with pneumonia having a burdened premorbid background ($p < 0.001$) in contrast to children in group 1. Development of measles pneumonia was accompanied by prolongation of the disease periods, more pronounced manifestations of intoxication syndrome ($p<0,05$), catarrhal manifestations ($p<0,05$), compared to patients with measles in group 1 (without the pneumonia development); signs of respiratory failure, decreased levels of SaO_2, against the background of measles anergy development, which was manifested by pronounced leukopenia, at the same time, comparing with the literature, it should be noted that the number of leukocytes in patients with measles in other studies remained within the normal range [1]. Pathohistological examination revealed signs of interstitial pneumonia with giant cell metaplasia of the alveolar epithelium, which is typical for the lesion of the measles virus [10].

Conclusions

1. During the 2018-2019 epidemic season there was a high incidence of measles in Ukraine and Vinnitsa region in particular.

2. Children from 6 to 17 years of age were more likely to suffer from measles, 81% of them were not vaccinated against measles. Among the complications, pneumonia was most commonly diagnosed (20%).

3. Interstitial measles pneumonia is by 37.44 times more likely to occur in measles patients with a burdened premorbid background (CI – 4.73; 296.53; p <0.00001). The mean age of patients with pneumonia is 5.75±3.79. The development of pneumonia is accompanied by a longer period of catarrhal manifestations (p <0.05), intoxication syndrome (p <0.05), with more frequent hectic fever (p <0.001); and the rash period is prolonged (p <0.05). In the vast majority of children (90%) the I degree respiratory failure occurs. In 37% of children a decrease in the SaO_2 level below 95% is reported. In the analysis of hemograms in patients with pneumonia, leukopenia is determined much more frequently (p <0.001), with a left shift diagnozed in the leukocyte formula.

4. A case of V degree measles pneumonia (mortality risk 29.2%), had a fatal outcome in the study, with the morphological and histological changes revealed in the respiratory tract of children with complicated disease course, which are characterized by the epithelium metaplasia into multilayer flat; giant cell metaplasia of the alveolar epithelium; abundant infiltration of the inter-alveolar septum with polymorphocellular infiltrate, with numerous parietal hyaline masses (hyaline membranes).

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Реферати

КОРОВА ПНЕВМОНІЯ У ДІТЕЙ: КЛІНІКО-МОРФОЛОГІЧНІ ОСОБЛИВОСТІ ПЕРЕБІГУ

Незгода І.І., Гаврилюк А.О., Асауленко А.А., Холод Л.П., Онофрійчук Є.С., Науменко О.М.

В статті наведені результати ретроспективного аналізу історій хвороб 96 хворих з діагнозом кір, з детальним вивченням перебігу захворювання і аналізом клініко-анамнестичних даних. Перебіг корової інфекції супроводжувався ознаками інтоксикаційного синдрому, наявністю класичної катаральної тріади (кашель, нежить та кон'юнктивіт), та синдромом екзантеми. Більшість дітей, що захворіли, не вакциновані проти кору. У хворих на кір мав місце ускладнений перебіг з проявами корової пневмонії, як найбільш частого ускладнення при даній патології. Морфологічні та гістологічні зміни легень у дітей з важким перебігом кору характеризувались рясною інфільтрацією як міжальвеолярних перетинок, так і просвітів альвеол поліморфноклітинним інфільтратом, який складався з нейтрофільних лейкоцитів, еозінофілів, лімфо-гістіоцитів, з чисельними пристінковими гіаліновими масами (гіалінові мембрани). Мала місце гігантоклітинна метаплазія альвеолярного епітелію.

Ключові слова: кір у дітей, пневмонія, патоморфологічні зміни, гістологічні дослідження.

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КОРЕВАЯ ПНЕВМОНИЯ У ДЕТЕЙ: КЛИНИКО-МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ТЕЧЕНИЯ

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В статье приведены результаты ретроспективного анализа историй болезней 96 больных с диагнозом корь, с детальным изучением течения заболевания и анализом клинико-анамнестических данных. Течение коревой инфекции сопровождалось признаками интоксикационного синдрома, наличием классической катаральной триады (кашель, насморк и конъюнктивит) и синдромом экзантемы. Большинство заболевших детей не 93акцинированы против кори. У больных корью имело место осложненное течение, с проявлениями коревой пневмонии, как наиболее частого осложнения при данной патологии. Морфологические и гистологические изменения легких у детей с тяжелым течением кори характеризовались обильной инфильтрацией как межальвеолярных перегородок, так и просветов альвеол полиморфноклеточным инфильтратом, который состоял из нейтрофильных лейкоцитов, эозинофилов, лимфо-гистиоцитов, с многочисленными пристеночными гиалиновыми массами (гиалиновые мембраны). Имела место гигантоклеточная метаплазия альвеолярного эпителия.

Ключевые слова: корь у детей, пневмония, патоморфологические изменения, гистологические исследования.

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