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## Laboratory and clinical peculiarities of the measles course in adult patients against the background of the use of a ribonucleic acid medicine in a comprehensive approach to treatment during the 2017-2019 outbreak period

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### Abstract

Vaccine-controlled viral diseases require a deeper study of the pathogenesis and immunological component. When performing this work, we've set the following goals: to study and distinguish the clinical and laboratory peculiarities of the measles course in adults, to describe the method of forecasting severe and complicated forms of the disease, as well as the possibility of using the ribonucleic acid medicine in the comprehensive treatment of the studied patients. During the performance of the work, there were analyzed 32 cases of measles in people of working age. Among the patients there were 6 (18.75%) people who confirmed the presence of two doses of the MMR vaccine. At the phase of the admission to the hospital, patients were divided into two groups, and they were compared according to the severity of the disease. The group I of patients received basic therapy; group II, in addition to basic therapy, received a ribonucleic acid medicine as an etiotropic agent. Evaluation of the clinical picture, hematological data, calculation of endogenous intoxication indices was performed at the phase of admission to the hospital, as well as during the third and fifth days of treatment. In the course of the study, the average severity of the disease was determined in most patients—27 (84.4%), and 5 (15.6%) patients—had severe disease. In all patients with measles, at the early stage of the disease, there was a significant increase in the integrative indices of endogenous intoxication: LII, ILS, RINM, NI, II, and IK. This was accompanied by a violation of immunological reactivity (increased ILS and decreased ILG) and an active adaptive response of the body (decrease in RIEL). When evaluating clinical data during the third and fifth days of the disease, it was noted that the main clinical manifestations of the disease subsided relatively faster in patients of the group II in contrast to the patients of the group I. A severe course of the disease was registered in 4 (25%) cases in patients of the group I, in 1 (6.25%) case in patients of the group II ( $p < 0.05$ ). The average length of hospital stay in patients of the group II was  $7.8 \pm 0.8$  days against  $9.2 \pm 0.7$  days of the patients of the group I ( $p < 0.05$ ). Integrative indices of endogenous intoxication against the background of the use of the ribonucleic acid medicine during the 3<sup>rd</sup> and 5<sup>th</sup> day of the disease had significant differences in the compared groups of patients, indicated the fading of the inflammatory reaction, activation of factors of a specific immunological response, and reduction of the extent of the endogenous intoxication syndrome. The application used by us for calculating indices of endogenous intoxication is a convenient and accessible method of visualization of pathogenetic and immunological processes of a viral disease, it makes it possible to influence these processes with medications and adjust therapy in a timely manner, and it is also a way of predicting possible complications.

**Keywords:** Measles, endogenous intoxication syndrome, indices of endogenous intoxication

### Introduction

Measles is a vaccine-controlled, highly contagious infectious disease characteristic of childhood, which nevertheless causes large-scale outbreaks in the countries of Europe and Asia [1-4] and has a certain percentage of mortality [1-5]. The problem of measles remains relevant, as there are many questions that need to be answered: the specifics of the disease in people of working age, measles in vaccinated people and those who have previously suffered from measles, the specifics of the immunological response, the problem of “immunological amnesia”, and, of course, the question of the treatment of measles patients.

The pathogenesis of a viral disease in which endogenous intoxication syndrome (ESI) plays a key role, is worthy of attention [6, 7, 17]. As a result of the integrated action of the virus in the cell, metabolic processes are disrupted, toxins of endogenous and exogenous origin, pyogenes, products of distorted metabolism and inflammatory mediators in non-physiological concentrations accumulate in various biological environments, which causes the clinical-laboratory changes that characterize ESI [8, 17]. According to the authors, the use of ribonucleic acid in the complex treatment of viral infections has a positive effect on the rate of recovery, as it suppresses the interaction of the virus with cell receptors due to conformational changes of the corresponding surface antigens [9, 10], has a membrane-stabilizing effect and inhibits oxidative processes. Therefore, when performing this work, we've set ourselves several tasks: to analyze the clinical-laboratory peculiarities of the course of measles in adult patients according to the data of the CNPE "Ivano-Frankovsk Regional Clinical Infectious Disease Hospital of the Ivano-Frankovsk Regional Council" (CNPE IF RCIDH IFRC), Ivano-Frankovsk, Ukraine, to determine the degree of endogenous intoxication and to find its connection with the severity of the course of the main disease, to study the effect of the ribonucleic acid medicine on the effectiveness of treatment.

### Research Methodology

There were analyzed 32 cases of measles in adult patients having undergone in-patient treatment at the CNPE IF RCIDH IFRC in January-March, 2019. All medical-diagnostic manipulations were carried out with the informed consent of the patients. The diagnosis was made on the basis of epidemiological anamnesis, complaints, characteristic clinical picture and specific laboratory research methods with the detection of anti-measles IgM antibodies in blood serum by enzyme immunoassay (ELISA).

At the stage of hospital admission, patients were divided into two groups, comparable by the severity of the disease. Patients of group I (16 people) received basic therapy (detoxification agents, anti-inflammatory agents, proteolysis inhibitors, hepatoprotective agents, antihistamines, antitussives, decongestants, and vitamin A); patients of group II (16 patients) in addition to basic therapy, as an dextrotropic agent, received ribonucleic acid medicine per os 500 mg 3 times a day for 7 days.

At admission, as well as during the third and fifth days of treatment, clinical analysis of peripheral blood was evaluated in patients of both groups, based on the results of which integrative hematological indices were calculated according to standard formulas and their statistical processing was performed to assess the severity of endogenous intoxication syndrome (ESI).

To calculate indices of endogenous intoxication, as well as to assess the severity of the disease, we've used the Android application "Indices of Endogenous Intoxication" (Utility Model Patent UA 123646, owner of the invention Sumy State University Sum DU, dated March 12, 2018) [11,16].

The criteria for exclusion from the study were: clinical-anamnestic data (hospitalization later than 6 days after the onset of the disease); mild measles; laboratory data (negative ELISA test results).

All the received data were entered into the "Individual registration form" developed for patients with measles. The

results of research and observation were processed with the help of computer programs Microsoft Office Excel 2010, Statistica 10 and an online calculator (<http://medstatistic.ru/calculators/calchit.html>).

### Results and Discussion

There were 17 women (53.12%) and 15 (46.88%) men among the examined patients. The age of the patients ranged from 18 to 68 years, the average age was  $32.16 \pm 2.39$  years. Hospitalization of patients with measles of moderate degree of severity was during the  $3.26 \pm 0.06$  days of the disease, with the severe degree during the  $4.85 \pm 0.19$  days of the disease. The largest number of appeals to the hospital was registered at the beginning of January, 2019–18 (56.25%) patients.

Among the examined people, 19 (59.37%) patients—are residents of the city of Ivano-Frankovsk, 2 (6.25%) patients are residents of towns in the regional centers, and 11 (34.77%) patients are residents of rural areas of the respective regions. As for the vaccination status of the examinees—6 (18.75%) people—had received two doses of the MMR vaccine on the basis of anamnesis and documented this fact, 18 (56.25%) hospitalized patients were unvaccinated, and 8 (25%) people had unknown vaccination status. There were 21 (65.6%) patients indicating the previous contact with measles patients. The average severity of the course of the disease was found in most patients during the study—27 people (84.4%), 5 people (15.6%) had a severe disease.

For patients with a severe course of the disease, a combination of complications in the respiratory and digestive organs was characteristic. Upon admission, the patient complained of a fever up to  $40^{\circ}\text{C}$ , pronounced general weakness, headache, body aches, runny nose, lacrimation, burning in the eyes, dry intrusive cough, shortness of breath at rest, discomfort when swallowing, and a rash on the body accompanied by itching, nausea and vomiting up to 1-4 times a day. When studying the clinical picture of the course of the disease, certain peculiarities were noted: in addition to the typical enanthema, 4 (80%) patients with a severe course of the disease had ulcerated elements on the mucous membrane of the oral cavity, type – aphthous stomatitis at the base of the gums and the inner surface of the lips. The patients' faces and eyelids were pasty, swollen. During indirect pulse oximetry, a drop in  $\text{SpO}_2$  up to 93-88% was noted, auscultatory breathing with a harsh tone was observed in the lungs, and in 3 (60%) patients at the stage of admission, and crepitus and moist scattered riles were heard. The maculopapular rash had a generalized character with a hemorrhagic component (positive Pasta's symptom). Hepatosplenomegaly was objectively detected in 3 (60%) patients.

In the general blood test upon admission in patients with a severe course of the disease, leukopenia was noted from  $4.3$  to  $2.6 \times 10^9$  g/l with a pronounced rod-nuclear shift to the left up to 22-29% and an accelerated ESR of 20-34 mm/h. Laboratory changes in the general blood analysis towards lymphocytosis were recorded during the  $4.61 \pm 0.87$  day of the disease. In the biochemical blood analysis, hypoproteinemia up to 51-53 g/l due to hypoglobulinemia, an increase in the activity of transaminases ALT  $162.68 \pm 28.14$  units/l, AST  $119.47 \pm 21.65$  units/l and an increase in the level of  $\alpha$ -amylase up to  $6.49 \pm 0.56$  units/l.

In patients with a moderately severe course of the disease upon admission, there was observed the following: in 65% of cases, patients complained of nausea, and in 7.5% of cases –

one-time vomiting. Objectively, moderate pastiness of the eyelids and face, an increase in the occipital and submandibular groups of lymph nodes, a rash of a generalized nature with a tendency to merge and in 3.24% of cases with a hemorrhagic component were noted. The structure of complications was dominated by changes in the organs of the chest cavity. In the general blood analysis there was a slight leukopenia and normocytosis with a neutrophilic shift to the left. In the biochemical blood analysis, the activity of ALT has increased up to  $89.57 \pm 22.56$  units/l, AST—up to  $78.54 \pm 13.72$  units/l, and the  $\alpha$ -amylase level—up to  $5.89 \pm 0.51$  units/l.

The nature of the distribution of complications in patients of groups I and II is as follows: acute catarrhal non-obstructive bronchitis – 12 (37.5%) cases, reactive hepatitis – 4 (12.5%) cases, viral and bacterial pneumonia—5 (15.62%) cases, deficiency anemia of mild and moderate severity—5 (15.62%) cases, reactive pancreatitis—4 (12.5%) cases, bacterial conjunctivitis—2 (6.66%) cases, aphthous stomatitis—5 (12.5%) cases, subconjunctival hemorrhage—1 (3.12%) case, otitis media—1 (3.12%) case, pleurisy—1 (3.12%) case, sinusitis—1 (3.12%) case.

During hospitalization, a significant increase in the leukocyte index of endogenous intoxication (LII) was determined – in  $4.2 \pm 0.23$  patients of both groups compared to normal values ( $p < 0.05$ ), indicating the activation of tissue lysis processes. We've noted that this index correlated with the rapid rate of development of complications in patients with a severe course of measles: viral-bacterial pneumonia, reactive hepatitis and pancreatitis. The hematological index of intoxication (HII) has significantly increased  $3.6 \pm 0.42$ -fold in the studied patients compared to normal values ( $p < 0.05$ ). The index of leukocyte shift (ILS) has increased  $3.1 \pm 0.18$ -fold indicating an active inflammatory process and violation of immunological tolerance.

The Krebs index (IK) significantly increased  $2.8 \pm 0.26$ -fold in both groups indicating the development of intoxication, an inflammatory reaction of moderate severity ( $p < 0.05$ ).

The lymphocyte-granulocyte index (ILG) decreased  $1.9 \pm 0.16$ -fold compared to the normal data, this index allows us to differentiate auto-intoxication from intoxication of infectious etiology. The index of ratio of neutrophils to monocytes (RINM) significantly increased  $2.2 \pm 0.51$ -fold ( $p < 0.05$ ). The obtained results indicate a clear shift of the leukocyte formula to the left, reflect the activation of a nonspecific immunological response to the present inflammatory process and the possible development of autoimmune reactions. A simultaneous increase in ILS and a decrease in ILG indicates the development of endogenous intoxication and a violation of immunological reactivity due to auto-intoxication of the body during the destruction of its own cells.

The nuclear index (NI) has increased  $11.7 \pm 0.84$ -fold indicating a severe inflammatory reaction, and it also reflects changes in white blood cells on antigenic and cytokine stimulation. An increase in NI indicates the presence of intoxication and a violation of the ability of neutrophils to eliminate antigen due to an increase in the number of young forms (rod-nuclear neutrophils) [10]. The presence of an acute inflammatory process reflects the intoxication index (II), which significantly increased  $24.7 \pm 0.63$ -fold ( $p < 0.05$ ). The index of immunological reactivity and the index of the ratio of lymphocytes and monocytes did not change significantly ( $p > 0.05$ ). The ratio index of eosinophils and lymphocytes

(RIEL) decreased  $2.1 \pm 0.51$ -fold ( $p > 0.05$ ), which reflects the predominance of the delayed-type reactions over immediate-type hypersensitivity and leads to the trigger of allergic mechanisms against the background of intoxication.

In all patients with measles, at the early stage of the disease, there was a significant increase in the integrative indices of endogenous intoxication: LII, ILS, RINM, NI, II, and IK. This was accompanied by a violation of immunological reactivity (increased ILS and decreased ILG) and an active adaptive response of the body (decrease in RIEL).

Clinical and laboratory data were evaluated in the studied groups during the 3<sup>rd</sup> and 5<sup>th</sup> day of the disease. The average duration of the intoxication syndrome in patients of the group II was  $3.1 \pm 0.34$  days, as opposed to  $4.2 \pm 0.41$  days in the patients of the group I; the body temperature decreased an average in  $2.9 \pm 0.34$  days, against  $3.8 \pm 0.26$  days in patients of the group I; catarrhal phenomena lasted  $2.6 \pm 0.28$  days in patients of the group II, against  $3.3 \pm 0.34$  days in patients of the group I; cough bothered the patients of group II for  $4.6 \pm 0.32$  days, against  $6.1 \pm 0.29$  days in patients of the group I; the rash lasted for  $4.6 \pm 0.38$  days in the patients of the group II, against  $5.1 \pm 0.42$  days in the patients of the group I ( $p < 0.05$ ). The average length of stay in the hospital of patients of the group II was  $7.8 \pm 0.8$  days, against  $9.2 \pm 0.7$  days of patients of the group I ( $p < 0.05$ ).

Analyzing the indices of peripheral blood, the following was noted: during the third day of treatment, the index of leukocyte intoxication (LII) has increased at 85% in the group I, against 65% in the group II; during the fifth day – an increase of 45% in the group I, against 25% in the group II ( $p < 0.05$ ). The obtained results were correlated with the nature of complications in the studied groups: the development of viral-bacterial pneumonias in patients of the group I—in 4 (25%) cases, in patients of the group II—in 1 (6.25%) case ( $p < 0.05$ ). The hematological index of intoxication has gradually decreased at 26% during the third day of the study in group II, against 19% in group I; and at 57% during the fifth day of observation in patients of group II, against 28% in patients of group I ( $p < 0.05$ ). A significant decrease in ILS from baseline data, was noted only during the fifth day of observation at 23% in patients of group I and at 34% in patients of group II, which indicates that the activity of the inflammatory process has subsided. IK and RINM were significantly reduced during the fifth day of the disease at 12% in patients of the group I against 22% in the patients of the group II, indicating the curtailment of the inflammatory process and a decrease in the activity of nonspecific immune response factors. NI during the third day of the disease decreased at 8% in patients of the group I, and at 13% in the patients of the group II; during the fifth day – a decrease at 16% in the group I, against 21% in the group II.

The obtained laboratory data clearly correlate with the dynamics of changes in the clinical picture of measles in patients. Comparing the obtained results in the groups, it is worth noting that at the early stage of measles, there is a sharp suppression of immunological reactivity because of auto-intoxication, due to the destruction of own cells and an increase in the number of cells producing cytokines. Visualization of the degrees of ESI at the early stage of the disease and in its dynamics, gives a clear understanding of the degree of activity of the inflammatory process and the state of immunological reactivity in each patient, in particular, regardless of vaccination status, which coincides with the

opinions of leading specialists [13, 14, 15].

## Conclusions

Therefore, the following peculiarities can be distinguished among adult patients, who were treated in the inpatient treatment center of the CNPE IF RCIDH IFRC in Ivano-Frankovsk in January-March, 2019 with a diagnosis of measles: the patients were mainly young people, city residents who had not been previously vaccinated with the MMR vaccine. In the structure of complications, damage to organs of the respiratory and digestive systems prevailed, which indicates the distinctive peculiarities of the course of measles in adults from the typical clinical picture. The used Android application allows us to speed up and visualize the degree of severity of endogenous intoxication and the body's ability to an effective immunological response at the stage of the patient's admission to the medical institution and in the dynamics. A clear connection was determined between the degree of severity of endogenous intoxication and the nature and rate of development of complications. All in all, this makes it possible to choose optimal patient's management tactics and timely corrections to the treatment regimen at an early stage of the disease. The use of the ribonucleic acid medicine in the scheme of treatment of adult patients with measles shortens the duration of the main clinical manifestations and reduces the frequency of complications of the disease.

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