

ABSTRACT

Veklich K. A. The Role of humoral immune factors in the development, clinical course of measles infection and the occurrence of complications. – Qualification scholarly paper: a manuscript.

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The aim of the study is to determine the nature of immune rearrangements in patients with measles infection of varying severity, their prognostic significance in the severity of the clinical course of measles infection and the development of complications, and the relationship of immune changes with the level of expression of Toll-like receptors type 9.

In the dissertation work the features of immunological rearrangements in patients with measles infection of varying severity, their prognostic significance in the severity of the clinical course of measles infection and the development of complications, and the relationship of immune changes with the level of expression of Toll-like receptors type 9 were studied.

A comprehensive clinical and laboratory examination of 108 patients with measles infection was performed, who were divided into groups: group 1-patients with acute measles infection of moderate severity, who had no complications and were treated in the general department; group 2-patients with acute measles infection of moderate severity, who had community-acquired pneumonia and were treated in the general department; group 3 – patients with acute severe measles infection, who had no complications and were treated in the intensive care unit; group 4 – patients with acute severe measles infection, who had community-acquired pneumonia and were treated in the intensive care unit.

In the control group 20 practically healthy volunteers, similar in age and gender, who did not have exclusion criteria were included. The inclusion criteria for patients into the study were: the presence of clinical manifestations of measles infection; age from 18 to 40 years; signed informed consent of the patient to

participate in the study. The exclusion criteria were: the presence of concomitant acute and chronic diseases in the acute and sub - and/or decompensation stages; immunosuppressive and autoimmune diseases; taking immunosuppressive drugs; performing surgical interventions 6 months before hospitalization for measles; giving birth 6 months before hospitalization for measles.

The observed groups were randomized and homogeneous in terms of age and disease severity.

On the day of admission to the hospital and on the 10th day of hospital stay, simultaneously with generally accepted laboratory tests special studies were performed: determination of interleukin levels (IL-1 β , IL-4, IL-6, IL-10), interferons alpha and gamma, general and virus-specific IgE, IGA, IgM, IgG with determination of avidity of the latter, autoantibodies to native DNA (ADNA-2), liver and kidney microsomes (anti-LKM-1) and antibodies to phospholipids of cell membranes, activity of the complement system and its C-3 component, small, medium and large circulating immune complexes, as well as the levels of Toll-like receptors type 9 expression on immunocompetent cells of peripheral blood.

Typical clinical manifestations of the disease observed in 100 % of patients included fever to febrile and high degrees, general weakness, headache, lymphadenopathy, and the development of exanthema. The development of exanthema was observed in 100 % of patients from groups 3 and 4 who had severe disease, and in 15 % and 30 % of patients from groups 1 and 2, respectively. Sore throat was a constant typical symptom in patients from groups 3 and 4 and was observed in 100 % of cases, in group 1 this symptom was detected in 70 % of patients (14 people), in group 2 – in 85 % (17 people). Scleral subictericity was recorded in 1 patient (11.1 %) from group 4. Injection of scleral vessels and their hyperemia was observed only in patients with severe disease – in 2 patients (12.5 %) from group 3 and in 5 (55.5) from group 4. So, typical clinical signs of the onset of measles infection, which were detected in most of the examined patients, included manifestations of intoxication syndrome, exanthema syndrome and lymphadenopathy.

When analyzing the data of a clinical blood test, it was found that the disease of moderate severity without complications develops against the background of lymphocytosis, a decrease in the absolute and relative number of neutrophils, and relative leukopenia with a tendency to normalization of indices in dynamics. Measles infection of moderate severity with pneumonia is characterized by minor leukocytosis, an increase in the relative and absolute number of neutrophils against the background of lympho - and monopenia, and an increase in ESR with a tendency to normalization of indices in dynamics. The severe course of measles infection is characterized by severe leukocytosis, an increase in the absolute and relative number of neutrophils, a significant increase in ESR, lympho - and monocytopenia, and has a rather weak dynamics of normalization of indices.

The study of Leukocyte indices of cellular reactivity (LICR) demonstrates the relationship between the severity of measles infection and the development of pneumonia with the indicators of clinical blood analysis – the levels of white blood cells, rod - and segmentonuclear neutrophils, lymphocytes and monocytes. It was shown that measles infection of moderate severity without complications is associated with a statistically significant decrease in the LSI and a statistically significant increase in LI at the beginning of the disease with a tendency to normalization in dynamics. The development of a moderate course of the disease with the development of pneumonia is characterized by a statistically significant increase in the LSI at the beginning of the disease with a tendency to normalization in dynamics, a statistically significant decrease in the LI with an increase in dynamics above the indicators of the control group. A severe disease without complications is observed under the condition of a statistically significant increase in the LSI at the beginning of the disease and its increase in dynamics, a statistically significant decrease in the LSI at the beginning of the disease with a downward trend. Severe disease with the development of complications develops against the background of a statistically significant increase in the LSI at the beginning of the disease and its increase in dynamics, a statistically significant decrease in LI, which tends to further decrease in dynamics.

It was found that a moderate measles infection develops against the background of an increase in platelet levels and their activity without significant disorders of the coagulation system, which leads to early and significant activation of other parts of the immune system, while a severe disease is observed with thrombocytopenia and low platelet activity with hyperaggregation, which can pose a threat of thrombosis.

When assessing the nature of the cytokine response of patients to measles infection, it was demonstrated that the severity of measles infection and the development of complications are associated with the levels of pro - and anti-inflammatory cytokines, $INF\alpha$ and $INF\gamma$ in the blood serum at the beginning of the disease and the dynamics of an their levels increase.

When studying the nature of the specific humoral immune response of patients involved in the study, it was demonstrated that measles infection in the adult population develops against the background of low titers of specific antibodies and their low avidity.

The study of the nature of changes in the complement system, the levels of total immunoglobulins and circulating immune complexes in patients involved in the study demonstrated a decrease in the activity of complement and, in particular, the C3-component of complement and an increase in the levels of total immunoglobulin E and small, medium and large circulating immune complexes.

Analysis of autoimmune reactions of patients with measles infection of varying severity showed that with the development of measles infection against the background of activation of general and specific immunity, activation of autoimmune reactions is observed. In all 4 groups of patients, the levels of autoantibodies to native DNA (ADNA2), liver and kidney microsomes (anti-LKM-1), and cell membrane phospholipids did not exceed the reference values. In severe cases of the disease with pneumonia, borderline values of autoantibodies were observed in a significant number of patients (66 %).

When studying the expression features of Toll-like Type 9 receptors on immunocompetent cells of peripheral blood of patients with cow infection, it was

found that in the moderate course of measles infection, a higher level, compared with healthy individuals, of TLR9 expression is observed ($p < 0,05$), and in the severe course of infection, a lower level, compared with healthy individuals, of expression of these pattern-recognizing receptors.

A Pearson correlation analysis performed on the day of admission showed a direct correlation between TLR9 expression levels and serum levels of interferon alpha, interferon gamma, and pro-inflammatory cytokines (IL-1 and IL-6). An inverse correlation was established with respect to anti – inflammatory cytokines – interleukins 4 and 10.

The conducted mathematical modeling of the length of stay of patients with measles infection in the hospital shows that it largely depends on the increase in the level of $INF\alpha$. Determining the level of the indicator on the day of patient admission to the hospital will optimize and improve the quality of medical care, calculate and rationalize treatment costs, and reduce the duration of inpatient treatment when using immunocorrective therapy.

The scientific novelty of the results obtained consists in deepening existing and obtaining new data on the role of the immune system in the development, course of measles infection and the occurrence of complications.

For the first time, based on the obtained data, an algorithm for monitoring leukocyte indices of cellular reactivity (LICR), cytokine levels (IL-1, IL-4, IL-6, IL-10, $INF\alpha$, $INF\gamma$), virus-specific IgG antibodies and their avidity was developed to predict the severity of measles infection and the development of complications on the basis of which a Certificate of copyright for a «Scientific literature work «The using a combination of indicators of the levels of an increase in the levels of interferons alpha and gamma, avidity of class G immunoglobulins and changes in the indicators of the blood leukocyte shift index in predicting the severity of measles infection» No. 102652 dated 17.02.2021.

The practical significance of the obtained results lies in the fact that based on the obtained results, a diagnostic algorithm has been developed and proposed for implementation in healthcare practice, which, taking into account clinical and

immunological data at the beginning of the disease, allows predicting the severity of measles infection with high probability.

In severe cases of measles to prevent the development of autoimmune pathology it is recommended to study the level of autoantibodies to phospholipids of cell membranes, IgG to microsomes of the liver and kidneys (anti-LKM-1) and IgG to native DNA (ADNA-2).

Mathematical prediction of the length of hospital stay of patients based on the nature of their immunoreactivity is proposed.

Studies have shown that individuals with a low titer of protective anti-measles IgG antibodies and their low avidity are at risk for measles infection. These individuals are recommended to be vaccinated against measles.

Key words: measles, cytokines, immunoglobulins, autoantibodies, Toll-like receptors, circulating immune complexes, complement, correlation analysis, mathematical modeling.