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The dynamics of TNF- α and IFN- γ content in adult patients with measles depending on the severity of the disease

O. V. Riabokon, S. O. Bilokobyla, Yu. Yu. Riabokon, N. V. Onishchenko

Zaporizhzhya State Medical University
Department of Infection Diseases

Abstract

Background. Measles is an acute viral infection, predominantly of childhood ages. However, in recent years, the incidence of measles among adults has significantly increased, with the development of a severe and complicated course of the disease.

Materials and methods. The study included 175 patients with measles and 30 healthy people. The quantitative content of TNF- α and IFN- γ in blood serum was determined by enzyme-linked immunosorbent assay. Statistical processing was performed in program "STATISTICA for Windows 13" (StatSoft Inc., No. JPZ804I382130ARCN10-J).

Results. A study of 175 measles patients found the frequency and spectrum of complications in adult patients depending on the severity of the disease and dynamics of TNF- α and IFN- γ level in blood serum. It is shown that frequency and range of complications in adult patients with measles depends on the severity of the disease. Patients with severe measles were more likely to develop complications from the respiratory system ($p < 0.01$) due to the formation of pneumonia ($p = 0.0001$) and from the gastrointestinal tract with more frequent development of hepatitis ($p = 0.0001$) and enteritis ($p = 0.0001$), compared with

moderate patients. In patients with severe measles, content of TNF- α in blood serum is the highest and exceeds both corresponding rate of healthy individuals ($p < 0.05$) and measles patients with moderate course ($p < 0.05$). Higher levels of TNF- α in the serum of measles patients during rash period are associated with severe course of the disease ($p = 0.008$). At the time of hospitalization of adult patients with measles during the rash IFN- γ content in the serum is higher ($p < 0.05$) than in healthy individuals, both in patients with severe ($p < 0.05$) and moderate course of measles ($p < 0.05$). In the dynamics of IFN- γ content in the serum patients of both study groups decreases ($p < 0.05$), compared with hospitalization, and at the time of discharge is not statistically different from that of healthy people ($p > 0.05$).

Conclusions. Patients with severe measles compared with moderate measles patients more likely developed complications from respiratory system ($p < 0.01$) and gastrointestinal system ($p < 0.01$). In patients with severe measles, content of TNF- α in blood serum is highest that corresponding rate of healthy individuals ($p < 0.05$) and patients with moderate course ($p < 0.05$). At the hospitalization time during the rash IFN- γ content in the serum is higher ($p < 0.05$) than in healthy individuals, both in patients with severe ($p < 0.05$) and with moderate measles ($p < 0.05$).

Key words: measles in adults; severity; cytokines.

Introduction. According to WHO in 2017-2010 in European countries, despite the widespread use of measles vaccine, there was a significant increase in measles patients [1, 2]. Periodic epidemic rises in measles are explained by the accumulation of susceptible populations due to shortcomings in immunoprophylaxis, which led to a decrease in collective post-vaccination immunity [3]. Studies in recent years point out that a feature of the epidemic rise of measles in 2017-2019 is the predominance among sick adults, whose share exceeds 52% [4] or even 73% [5].

It is known that measles in adults is associated with a high risk of complications [4, 5], immunopathogenetic mechanisms formation of which are still being studied. It is noted that immunological changes that occur in response to measles virus replication are characterized on the one hand by immunosuppression, severity of which is associated with the development of complications. However, on the other hand, it is noted that measles virus paradoxically causes induction of strong virus-induced specific immunity [6]. The state of the cytokine system is particular importance in the formation of immune response, as cytokines control processes of proliferation, differentiation and functional activity of immunocompetent cells [7]. It is known that disruption of anti-inflammatory cytokine production can lead to a

violation of anti-infective protection and lead to a deepening of the direct viruses action on cells various organs and systems [8, 9]. Therefore, in our opinion, it is important to clarify the role of such major proinflammatory cytokines as tumor necrosis factor α (TNF- α) and interferon- γ (IFN- γ) in the formation of varying severity of measles in adults.

The aim of the study is to determine the dynamics of TNF- α and IFN- γ content in the serum of adult patients with measles depending on the severity of the disease.

Material and methods. The study included 175 patients with measles, who were treated at the Municipal Institution "Regional Infectious Diseases Clinical Hospital of Zaporizhia Regional Council". The age of patients ranged from 18 to 58 years, men were 81, women - 94. The diagnosis of measles was established according to WHO criteria (2013) [10]. Patients were divided into groups depending on the severity of the disease: 148 patients with moderate course; 27 patients - with severe measles. All patients were included in the study on a random basis and with informed consent. The content of TNF- α (Invitrogen, Austria) and IFN- γ (Invitrogen, Austria) in the blood serum of patients and 30 healthy individuals was determined by enzyme-linked immunosorbent assay at the Training Medical and Laboratory Center of Zaporizhia State Medical University (Professor AV Abramov).

Statistical data processing was performed in the program "STATISTICA for Windows 13" (StatSoft Inc., No. JPZ804I382130ARCN10-J). The Mann-Whitney method was used to assess the significance of differences in quantitative indicators. Relationships between traits were assessed by Spearman's correlation and gamma ratio.

Results. According to the results of our study, dependence of the frequency and spectrum of complications in adult patients with measles on the severity of the disease were established. Among hospitalized patients, presence of complications was recorded in 97 (65.5%) patients with moderate course against 27 (100%) patients with severe measles ($p < 0.01$). Analysis of complications spectrum showed that patients with severe measles were more likely to develop complications of the respiratory system ($p < 0.01$) due to the formation of pneumonia ($\chi^2 = 63.6$, $p = 0.0001$). The second most common was development complications of gastrointestinal tract with more frequent development hepatitis ($\chi^2 = 19.3$, $p = 0.0001$) and enteritis ($\chi^2 = 24.9$, $p = 0.0001$) in patients with severe measles, compared with moderate course of the disease (Fig. 1). It should be noted that complications from the central nervous system in the form of serous meningitis (1 - 3.7%) and from the organ of vision in the form of cyclitis (1 - 3.7%) were found only in patients with severe measles against absence of such complications in patients with moderate disease.

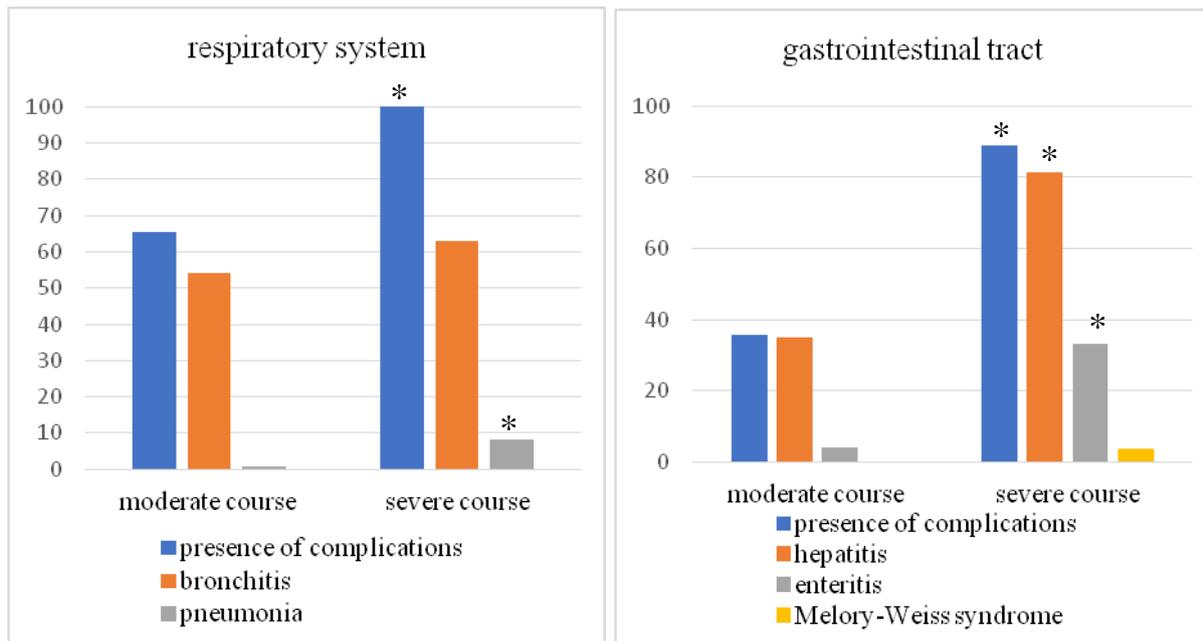


Figure 1. Spectrum and frequency of complications in adult patients depending on the severity of measles (* - the difference is significant compared with patients with moderate measles) ($p < 0,01$).

Analysis of TNF- α in the serum of adult patients with measles showed that at the hospitalization time during rash period, this figure was elevated in patients of both study groups, but level of increase clearly depended on the severity of the disease. Thus, in patients with severe measles, TNF- α content in the serum exceeded both the corresponding rate of healthy individuals ($p < 0.05$) and patients with measles with moderate course ($p < 0.05$). In the dynamics of the disease in patients with severe measles, TNF- α level in blood serum decreased ($p < 0.05$), compared with hospitalization, but at the discharge time remained higher ($p < 0.05$) than in healthy individuals. In addition, it should be noted that at the time of discharge, TNF- α level in blood serum of patients with severe course was 2.2 times higher than corresponding rate of patients with moderate course of the disease ($p < 0,05$) (Table 1). Using the statistical method of rank gamma correlation, a direct correlation was found between severity of measles and quantitative content of TNF- α in the serum of patients hospitalized during rash period ($p < 0.05$). Established correlations suggest an association of higher TNF- α levels in blood serum of measles patients during the rash with severe course of the disease (gamma ratio 0.38, $p = 0.008$).

Table 1. The dynamics of TNF- α and IFN- γ content in the serum of adult patients with measles depending on the severity of the disease, Me [Q25; Q75] pg / ml

Terms of examination	Healthy people (n=30)	Patients with measles	
		moderate course (n=148)	severe course (n=27)
TNF- α , Me [Q ₂₅ ; Q ₇₅] pg/ml			
At hospitalization	0,04 [0,02; 0,04]	0,06 [0,04; 0,44] ¹	1,73 [0,26; 4,48] ^{1,2}
At the discharge		0,06 [0,04; 0,14] ¹	0,13 [0,04; 3,54] ^{1,2,3}
IFN- γ , Me [Q ₂₅ ; Q ₇₅] pg/ml			
At hospitalization	0,09 [0,08; 0,20]	1,20 [0,18; 11,42] ¹	4,26 [0,70; 10,72] ¹
At the discharge		0,17 [0,08; 0,44] ³	0,09 [0,04; 0,31] ³

Notes: 1 - the difference is significant compared to healthy people ($p < 0,05$); 2 - compared to patients with moderate course ($p < 0,05$); 3 - compared to corresponding group at hospitalization ($p < 0,05$).

At the hospitalization time of adult patients with measles during rash period, content of IFN- γ in the serum was higher ($p < 0,05$) than in healthy individuals, both in patients with severe ($p < 0,05$) and moderate course of the disease ($p < 0,05$). During this observation period, IFN- γ level in blood serum of patients with severe course was 3.6 times higher than corresponding rate of patients with moderate course, but this difference was not statistically significant ($p > 0,05$). In the dynamics of the ongoing treatment, concentration of IFN- γ in the serum of both study groups patients decreased ($p < 0,05$), compared with hospitalization, and at the discharge time did not differ statistically from healthy people ($p > 0,05$) (Table 1).

Correlation analysis with detection Spearman's correlation coefficient showed the presence of correlations between content of the studied cytokines and hemogram of measles patients. Thus, the content of IFN- γ in blood serum had a direct correlation with relative content of rod-shaped leukocytes ($r = 0,38$, $p < 0,001$), relative content of lymphocytes ($r = 0,31$, $p < 0,01$), activity of alanine aminotransferase ($r = 0,25$, $p < 0,05$) and inverse correlation with the relative content of segmental leukocytes ($r = -0,32$, $p < 0,01$). The content of TNF- α in the serum was inversely correlated with relative content of blood lymphocytes ($r = -0,30$, $p < 0,05$).

Discussion. It is known that measles in adults is much more common than in children, leads to development severe course of the disease. The data of different researchers on the frequency and spectrum of measles complications in adults differ to some extent [11, 12, 13].

Among the complications of measles in adults, most researchers describe complications from the respiratory system and gastrointestinal tract [11, 12, 13, 14]. However, literature data on the incidence of pneumonia in adult patients range from 15% to 81% [11, 13], and the incidence of hepatitis range from 45% to 81% [13, 14]. According to our data, the incidence of pneumonia in adult patients with measles was 7.4%, while to confirm pneumonia we used only X-ray examination. According to our study, the incidence of hepatitis was 42.3% among hospitalized patients with measles, hepatitis diagnosed on the basis of the detected cytolytic syndrome.

It is known that with the development of secondary viremia, clinical symptoms appear, and maximum concentration of measles virus in the cells of lymphoid structures, respiratory system, gastrointestinal tract determines the features of clinical manifestations and the range of complications that occur [6]. The inflammatory process that develops in patients with measles is characterized as serous-macrophage and is accompanied by lymphocytic infiltration and vasculitis of small vessels of various organs and systems [15]. IFN- γ is one of the key cytokines involved in the development of systemic and local inflammatory and immunopathological reactions, which causes appearance of rash and clearance of measles virus [16]. However, in measles, acute phase is characterized by the formation of leukopenia in combination with high levels of this cytokine [17]. We found the highest levels of increased TNF- α and IFN- γ in the serum of adult patients with severe course of measles. The literature suggests that increase in the production of proinflammatory cytokines plays an important role in the formation of a more severe course of the disease by enhancing the aggregation of leukocytes with vascular epithelium, stimulating its procoagulant activity, involvement of effector cells in the area of inflammation [7].

Conclusions

1. The frequency and range of complications in adult patients with measles depends on the severity of the disease. Patients with severe course of measles were more likely to develop complications from the respiratory system ($p < 0.01$) due to the formation of pneumonia ($p = 0.0001$) and from the gastrointestinal tract with more frequent development of hepatitis ($p = 0.0001$) and enteritis ($p = 0.0001$), compared with moderate course of the disease.

2. In patients with severe measles, content of TNF- α in blood serum is highest and exceeds the corresponding rate of healthy individuals ($p < 0.05$) and patients with moderate course of measles ($p < 0.05$). Higher levels of TNF- α in the serum of patients with measles during the rash are associated with severe course of the disease (gamma ratio 0.38, $p = 0.008$).

3. At the hospitalization time of adult patients with measles during rash period, IFN- γ content in the serum is higher ($p < 0,05$) than in healthy individuals, both in patients with severe ($p < 0,05$) and with moderate measles ($p < 0,05$). In the dynamics of IFN- γ content in the serum of patients both study groups decreases ($p < 0,05$), compared with hospitalization, and at the time of discharge is not statistically different from that of healthy people ($p > 0,05$).

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