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Dynamics of TNF-α and IFN-γ in adult patients with measles depending on the development of complications

S. O. Bilokobyla[B,C,D], **O. V. Riabokon**[A,F], **Yu. Yu. Riabokon**[C,E], **N. V. Onishchenko***[C,E]

Zaporizhzhia State Medical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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***E-mail:** helicobacter1403@gmail.com

The aim is to define the dynamics of TNF-α and IFN-γ serum levels in adult patients with measles depending on the development of complications.

Materials and methods. An examination of 175 adult patients with measles revealed a range of complications and dynamics of serum TNF-α and IFN-γ depending on the development of complications. The serum contents of TNF-α (Invitrogen, Austria) and IFN-γ (Invitrogen, Austria) in patients and 30 healthy individuals were determined by enzyme-linked immunosorbent assay on the basis of the Training Medical Laboratory Center of Zaporizhzhia State Medical University.

Results. It was shown that the vast majority of hospitalized adult patients with measles developed complications (70.6 %) and these latter were predominantly respiratory (61.7 %) and gastrointestinal (44.0 %). In the period of measles rash, on day 4.8 ± 0.2 in the presence of complications, the serum TNF-α content was 11 times higher than that in healthy individuals ($P < 0.05$) and in patients with uncomplicated measles ($P < 0.05$), and did not differ from healthy individuals ($P > 0.05$) in the absence of complications. The development of measles complications in adult patients was associated with higher serum levels of TNF-α both at hospitalization ($P = 0.003$) and after 10 days of the disease ($P = 0.005$).

The serum content of IFN-γ in adult measles patients with rash at hospitalization on day 4.8 ± 0.2 exceeded that in healthy individuals both in the presence of complications ($P < 0.05$) and in uncomplicated measles ($P < 0.05$). The serum content of IFN-γ was 19.3 times ($P < 0.05$) higher in patients with complicated measles than that in patients without complications. High serum levels of IFN-γ were associated with the development of complications during acute period of measles ($P = 0.0001$).

Conclusions. Complications occurred in most hospitalized adult patients with measles (70.6 %), that was accompanied by more pronounced immunological changes. The development of measles complications in adult patients was associated with higher serum levels of TNF-α both at hospital admission on day 4.8 ± 0.2 (gamma 0.77; $P = 0.003$) and in the dynamics after 10 days of the disease (gamma 0.56; $P = 0.005$). Elevated serum levels of IFN-γ were associated with the development of complications during the acute period of measles (gamma ratio 0.46; $P = 0.0001$).

Ключові слова: кір у дорослих, ускладнення, цитокіни.

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Динаміка вмісту TNF-α та IFN-γ в дорослих, які хворі на кір, залежно від розвитку ускладнень

С. О. Білокобила, О. В. Рябоконь, Ю. Ю. Рябоконь, Н. В. Оніщенко

Мета роботи – з'ясувати динаміку вмісту TNF-α та IFN-γ в сироватці крові дорослих осіб, які хворі на кір, залежно від розвитку ускладнень.

Матеріали та методи. У результаті обстеження 175 дорослих хворих на кір визначили спектр ускладнень і динаміку вмісту TNF-α та IFN-γ в сироватці крові залежно від розвитку ускладнень. Концентрацію TNF-α та IFN-γ (Invitrogen, Austria) в сироватці крові пацієнтів і 30 здорових осіб визначали методом імуноферментного аналізу на базі Навчального медико-лабораторного центру Запорізького державного медичного університету.

Результати. Переважно в госпіталізованих пацієнтів діагностували ускладнення (70,6 %), здебільшого з боку дихальної системи (61,7 %) та шлунково-кишкового тракту (44,0 %). У період висипу кору (на 4,8 ± 0,2 дня хвороби) за наявності ускладнень уміст TNF-α в сироватці крові в 11 разів перевищує відповідний показник здорових осіб ($p < 0,05$) та хворих на кір без ускладнень ($p < 0,05$); якщо ускладнень не було, не відрізнявся від показника здорових осіб ($p > 0,05$). Розвиток ускладнень кору в дорослих асоціюється з вищим рівнем TNF-α в сироватці крові під час госпіталізації ($p = 0,003$) та в динаміці захворювання через 10 діб ($p = 0,005$).

Концентрація IFN-γ в сироватці крові дорослих хворих на кір під час госпіталізації (на 4,8 ± 0,2 дня хвороби) в період висипу перевищує показники здорових осіб і за наявності ускладнень ($p < 0,05$), і при неускладненому перебігу хвороби ($p < 0,05$). Найвищий вміст IFN-γ в сироватці крові визначили в пацієнтів із ускладненим перебігом кору; перевищення відповідного показника хворих без ускладнень – у 19,3 раза ($p < 0,05$). Високий рівень IFN-γ в сироватці крові асоціюється з розвитком ускладнень у період розпалу кору ($p = 0,0001$).

Висновки. У більшості госпіталізованих дорослих пацієнтів із кором виявили ускладнення (70,6 %), розвиток яких супроводжувався вираженішими імунологічними змінами. Виникнення ускладнень кору в дорослих асоціюється з вищим рівнем TNF-α в сироватці крові під час госпіталізації (на 4,8 ± 0,2 дня хвороби; гамма 0,77, $p = 0,003$) та в динаміці захворювання (через 10 діб; гамма 0,56, $p = 0,005$). Високий рівень IFN-γ в сироватці крові асоціюється з розвитком ускладнень у період розпалу кору (коефіцієнт гамма 0,46, $p = 0,0001$).

Динамика содержания TNF-α и IFN-γ у взрослых больных корью в зависимости от развития осложнений

С. А. Белокобыла, Е. В. Рябоконь, Ю. Ю. Рябоконь, Н. В. Онищенко

Ключевые слова: корь у взрослых, осложнения, цитокины.

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Цель работы – определить динамику содержания TNF-α и IFN-γ в сыворотке крови взрослых больных корью в зависимости от развития осложнений.

Материалы и методы. В результате обследования 175 взрослых больных корью установили спектр осложнений и динамику содержания TNF-α и IFN-γ в сыворотке крови в зависимости от развития осложнений. Содержание TNF-α (Invitrogen, Austria) и IFN-γ (Invitrogen, Austria) в сыворотке крови пациентов и 30 здоровых лиц определяли методом иммуноферментного анализа на базе Учебного медико-лабораторного центра Запорожского государственного медицинского университета.

Результаты. У подавляющего большинства госпитализированных пациентов отмечено развитие осложнений (70,6 %), чаще всего со стороны дыхательной системы (61,7 %) и желудочно-кишечного тракта (44,0 %). В период сыпи кори (на 4,8 ± 0,2 дня болезни) при наличии осложнений содержание TNF-α в сыворотке крови в 11 раз превышает соответствующий показатель здоровых лиц ($p < 0,05$) и больных корью без осложнений ($p < 0,05$); при отсутствии осложнений – не отличался от показателя здоровых лиц ($p < 0,05$). Развитие осложнений кори у взрослых ассоциируется с более высоким уровнем TNF-α в сыворотке крови при поступлении ($p = 0,003$) и в динамике заболевания через 10 дней ($p = 0,005$).

Концентрация IFN-γ в сыворотке крови взрослых больных корью при поступлении (на 4,8 ± 0,2 дня болезни) в период сыпи превышает показатели здоровых лиц и при наличии осложнений ($p < 0,05$), и при неосложнённом течении болезни ($p < 0,05$). Наибольшее содержание IFN-γ в сыворотке крови установлено у пациентов с осложнённым течением кори; превышение соответствующего показателя пациентов без осложнений – в 19,3 раза ($p < 0,05$). Высокий уровень IFN-γ в сыворотке крови ассоциируется с возникновением осложнений в период разгара кори ($p = 0,0001$).

Выводы. У большинства госпитализированных пациентов с корью диагностировали осложнения (70,6 %), развитие которых сопровождалось более выраженными иммунологическими изменениями. Развитие осложнений кори у взрослых ассоциируется с более высоким уровнем TNF-α в сыворотке крови при госпитализации (на 4,8 ± 0,2 дня болезни; гамма 0,77; $p = 0,003$) и в динамике заболевания (через 10 дней; гамма 0,56; $p = 0,005$). Высокий уровень IFN-γ в сыворотке крови ассоциируется с развитием осложнений в период разгара кори (коэффициент гамма 0,46; $p = 0,0001$).

Measles is a very contagious viral infection with a highly risk of severe complications. Due to a measles massive vaccination campaign in the early 2000s, the WHO has set goals to interrupt measles local circulation in the European Region [1]. Despite some progress made towards the measles elimination in the European Region, the epidemic process is still spreading quite rapidly [2]. Cyclical epidemics and emergence of local measles outbreaks are associated with an increase in the number of susceptible populations due to low immunization rates in previous years resulting in decreased post-vaccination immunity [3]. In 2017–2018, in European countries, including Ukraine, there was a significant increase in the incidence of measles [4]. A feature of measles in recent years is the predominance of adults among sick individuals, in particular, Germany reported 52 % [5], Italy – 73 % [6] and Belgium – 50 % of measles patients [7] over 15 years old.

The pathogenetic mechanisms of complications in measles patients are still unclear. The risk of measles complications is correlated with the severity of immunosuppression that develops in patients with measles. At the same time, a paradoxical induction of strong virus-induced specific immune response can be seen in measles virus infection followed by lifelong immunity [8]. The cytokine system state, a universal regulatory system of mediators that controls the processes of proliferation, differentiation, apoptosis, and functional activity of immunocompetent cells, is important in the immune response formation [9]. It is known that dysregulated production of anti-inflammatory cytokines can lead to a decrease in protection against infectious agents and increase the direct damaging effect of viruses on various organs and systems [10,11]. Therefore, the role of such major pro-inflammatory cytokines as tumor necrosis factor α (TNF-α) and interferon-γ (IFN-γ) in the measles complications development in adults deserves special attention.

Aim

The aim is to define the dynamics of serum TNF-α and IFN-γ quantitative contents in adult measles patients depending on the development of complications.

Materials and methods

In the study, 175 patients (81 males and 94 females) with measles aged between 18 and 58 years were examined. All patients received a treatment in the Municipal Institution "Regional Infectious Diseases Clinical Hospital of the Zaporizhzhia Regional Council" during 2017–2019. The diagnosis of measles was confirmed by clinical, epidemiological, and serological tests with the identification of anti-measles IgM according to the WHO criteria (2013) [12]. All the patients underwent traditional clinical, laboratory and instrumental examinations and were assigned to either a group with or without complications, 124 and 51 individuals, respectively. The patients were twice examined: at hospitalization on day 4.8 ± 0.2 of the disease and after 10 days of inpatient treatment. The serum contents of TNF-α (Invitrogen, Austria) and IFN-γ (Invitrogen, Austria) in the patients and 30 healthy people were determined by enzyme-linked immunosorbent assay at the Training Medical and Laboratory Center of Zaporizhzhia State Medical University, headed by MD, Professor A. V. Abramov.

Statistical data processing was carried out using the program Statistica for Windows 13 (StatSoft Inc., No. JP-Z804I382130ARCN10-J). Mann–Whitney U tests were used to compare continuous variables between the complication

Table 1. Frequency and spectrum of complications in adult patients with measles, abs. (%)

Indicator	Patients with measles (n = 175)
Uncomplicated course	51 (29.4 %)
Complicated course	124 (70.6 %)
Respiratory complications:	108 (61.7 %)
– bronchitis	97 (55.4 %)
– pneumonia	13 (7.4 %)
Gastrointestinal complications:	77 (44.0 %)
– hepatitis	74 (42.3 %)
– enteritis	15 (8.6 %)
– Mallory–Weiss syndrome	1 (0.6 %)
Eye complications	
– cyclitis	1 (0.6 %)
Central nervous system complications:	
– serous meningitis	1 (0.6 %)

Table 2. Dynamics of TNF-α and IFN-γ serum levels in adult patients with measles depending on the development of complications, Me [Q25; Q75], pg/ml

Time of examination	Healthy people	Patients with measles	
		With complications	Without complications
TNF-α, Me [Q25; Q75], pg/ml			
At admission	0.04 [0.02; 0.04]	0.44 [0.08; 2.17][1,2]	0.04 [0.04; 0.12]
After 10 days		0.07 [0.04; 1.52][1,3]	0.06 [0.04; 0.10][1]
IFN-γ, Me [Q25; Q75], pg/ml			
At admission	0.09 [0.08; 0.20]	4.83 [0.29; 12.86][1,2]	0.25 [0.13; 1.14][1]
After 10 days		0.14 [0.08; 0.58][3]	0.12 [0.08; 0.24]

Significant differences: **1** – compared to the healthy people (P < 0.05); **2** – compared to the patients without complications (P < 0.05); **3** – compared to the corresponding group at admission (P < 0.05).

group and the group without complications. Correlations between findings were evaluated using the Spearman test and gamma ratio.

Results

The study results showed that measles progressed with the development of complications in most adult patients (70.6 %). Respiratory complications prevailed (61.7 %), including acute bronchitis (55.4 %) and pneumonia (7.4 %). Almost one in two patients (44.0 %) had gastrointestinal complications, including hepatitis (42.3 %), enteritis (8.6 %), Mallory–Weiss syndrome (0.6 %). In some cases, adult patients developed measles-related visual impairments in a form of cyclitis (0.6 %) and central nervous system disorders manifested as serous meningitis (0.6 %) (*Table 1*).

Changes in the serum TNF-α content in adult measles patients were shown to be highly dependent on the complication presence at the time of hospitalization on day 4.8 ± 0.2 of the disease during the rash. For instance, in the presence of complications, the TNF-α level was 11 times higher than that in healthy individuals (P < 0.05) and patients with uncomplicated measles (P < 0.05). It should be noted that the serum content of TNF-α in patients with uncomplicated measles did not differ statistically from that in healthy people (P > 0.05) on day 4.8 ± 0.2. Within 10 days of follow-up, the serum content of TNF-α decreased (P < 0.05) in patients with complicated measles compared with hospitalization, but remained higher than in healthy individuals (P < 0.05) at the time of discharge (*Table 2*). Using the statistical method of gamma rank correlation, a direct correlation was found between the complicated measles course and the serum concentration of TNF-α in the patients on day 4.8 ± 0.2 of the disease and after 10 days of follow-up (P < 0.05). That is, the found correlations suggested that there was an association between complications development by patients with the highest serum levels of TNF-α both at admission (scale 0.77; P = 0.003), and in the disease dynamics (scale 0.56; P = 0.005).

Analysis of the serum IFN-γ content in adult measles patients in dynamics showed higher levels of this cytokine at the time of admission (P < 0.05) on day 4.8 ± 0.2 of the disease than those in healthy people, regardless of complication development (P < 0.05). However, the highest serum content of IFN-γ was in the patients with complicated measles, 19.3 times (P < 0.05) greater than the corresponding value of the patients without complications. It is worth noting that the significant increase in the serum IFN-γ content was short-term and decreased (P < 0.05) in the dynamics after 10 days of the disease in patients with complicated measles as compared to the admission level. The serum content of IFN-γ in patients of both study groups did not differ statistically from that of healthy people (P > 0.05) after 10 days in the dynamics (*Table 2*). A direct correlation between the complicated course of measles and the quantitative content of IFN-γ in patients at admission on day 4.8 ± 0.2 of the disease (P < 0.05) was found. These correlations proved an association between elevated serum levels of IFN-γ and the development of complications during acute period of measles (gamma ratio 0.46; P = 0.0001).

Using Spearman's analysis, significant correlations were found between the levels of studied cytokines and hemograms and laboratory indicators of adult measles patients. Namely, the serum content of IFN-γ was directly correlated with the number of band neutrophils (r = 0.38; P < 0.001), lymphocyte count (r = 0.31; P < 0.01), alanine aminotransferase activity (r = 0.25; P < 0.05) and inversely – with the number of segmented neutrophils (r = -0.32; P < 0.01). The serum TNF-α content was inversely correlated with the number of blood lymphocytes (r = -0.30; P < 0.05).

Discussion

Modern literature data [4–7] show that during the epidemic rise in the measles incidence in 2017–2019, there was a clear predominance of adults among sick individuals. It has been believed that measles in adults is accompanied by a severe course and the development of complications more often than in children. However, literature data on the incidence of measles complications in adults varies which might be due to different indications for hospitalization and different diagnostic methods used (computed tomography or X-ray examination) [13–15]. Among the most commonly diagnosed complications are respiratory and gastrointestinal [13–16]. However, according to various researchers, the incidence of pneumonia in adult patients ranges from 15.3 % [13] to 81 % [15], and the incidence of hepatitis – from 45 % [16] to 81 % [15]. Based on our study, the incidence of pneumonia in adult measles patients was 7.4 %, although it should be pointed out that we used only chest X-ray examination to confirm this complication. The results of our study have shown hepatitis in 42.3 % of

measles patients, which was diagnosed through cytolytic syndrome detection.

Immunological pathogenetic mechanisms of measles complications are currently being examined. It has been shown that the severity of immunosuppression in measles patients was correlated with the risk of complications [8]. In the conditions of secondary viremia, which is accompanied by the manifestation of clinical symptoms, measles virus reaches the maximum concentration in the cells of lymphoid structures, respiratory system, gastrointestinal tract, and eye epithelium, determining a spectrum of complications [8]. With the development of respiratory and gastrointestinal complications, which are the most common in measles patients, the inflammatory process is characterized as serous-macrophage and accompanied by lymphocytic infiltration and small-vessel vasculitis [17]. It is known that IFN-γ is one of the key cytokines, as it determines the formation of Th1-type immune response and is involved in the development of systemic and local inflammatory and immunopathological reactions that cause rash and measles virus clearance [18]. However, in measles, the acute phase differs from classical reaction and is characterized by the formation of leukopenia in combination with elevated levels of IFN-γ [19]. According to our study, the highest serum levels of TNF-α and IFN-γ were revealed in adult measles patients with complications. The literature suggest that increased production of pro-inflammatory cytokines plays an important role in the development of complications seen in a number of organs and systems by inducing leukocyte adherence to vascular epithelium, stimulating its procoagulant activity, involving effector cells in the inflammatory zone, thereby worsening immunopathological lesions in various organs [9].

We have determined in the disease dynamics a significant decrease in the content of studied cytokines after 10 days of treatment compared to the corresponding indicators at admission in patients with complicated measles, while the TNF-α content in this period remained significantly higher than that in healthy individuals. It is worth noting that in patients without complications, the content of TNF-α increased in the dynamics and became higher than that in healthy persons. In recent years, scientific literature has published the study results of other authors on the cytokine profile dynamics in adult measles patients. Thus, the study [20] analyzed the dynamics of pro-inflammatory and anti-inflammatory cytokine levels in adult measles patients considering two factors, namely severity of the course and the presence of complications. The study [20] has shown the highest level of serum IFN-γ in patients with moderate uncomplicated course in the dynamics of the disease, and the lowest one – in patients with severe course and pneumonia. This article presents our study results with no regard for the severity of measles. Nevertheless, we have also previously published the results of analysis [21,22] on the content of studied cytokines depending on the severity of measles, albeit without additional division into groups based on the presence of complications. Our results obtained analyzing the data in the measles dynamics, were to some extent in line with the study results [20], namely, the serum IFN-γ content in patients with severe course of the disease was found to be lower than that in patients with moderate course after 10 days of treatment [22].

Conclusions

1. Complications occurred in most hospitalized adult patients with measles (70.6 %) and were primarily related to the respiratory system (61.7 %) and gastrointestinal tract (44.0 %).

2. In the period of measles rash, on day 4.8 ± 0.2 of the disease with the presence of complications, the serum content of TNF-α was 11 times higher than that in healthy individuals ($P < 0.05$) and in patients with uncomplicated measles ($P < 0.05$), and did not differ from that in healthy individuals ($P > 0.05$) in the absence of complications. The development of measles complications in adult patients was associated with higher serum levels of TNF-α both at hospital admission on day 4.8 ± 0.2 of the disease (gamma 0.77; $P = 0.003$) and in the dynamics after 10 days (gamma 0.56; $P = 0.005$).

3. The serum IFN-γ content in adult measles patients at admission on day 4.8 ± 0.2 of the disease in the period of rash was higher than that in healthy individuals regardless of complications ($P < 0.05$). The highest serum content of IFN-γ was in the patients with complicated measles, 19.3 times greater ($P < 0.05$) than the corresponding value of the patients without complications. Elevated serum levels of IFN-γ were associated with the development of complications during the acute period of measles (gamma ratio 0.46; $P = 0.0001$).

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Information about authors:
Bilokobyla S. O., MD, Assistant of the Department of Infectious Diseases, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0002-5673-616X
Riabokon O. V., MD, PhD, DSc, Professor, Head of the Department of Infectious Diseases, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0002-7394-4649
Riabokon Yu. Yu., MD, PhD, DSc, Professor of the Department of Children Infectious Diseases, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0002-2273-8511
Onishchenko N. V., MD, PhD, Assistant of the Department of Infectious Diseases, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0001-7775-7296

Відомості про авторів:
Білокобила С. О., асистентка каф. інфекційних хвороб, Запорізький державний медичний університет, Україна.
Рябоконь О. В., д-р мед. наук, професор, зав. каф. інфекційних хвороб, Запорізький державний медичний університет, Україна.
Рябоконь Ю. Ю., д-р мед. наук, професор каф. дитячих інфекційних хвороб, Запорізький державний медичний університет, Україна.
Оніщенко Н. В., д-р філософії, асистентка каф. інфекційних хвороб, Запорізький державний медичний університет, Україна.

Сведения об авторах:
Белокобыла С. А., ассистент каф. инфекционных болезней, Запорожский государственный медицинский университет, Украина.

Рябоконь Е. В., д-р мед. наук, профессор,
зав. каф. инфекционных болезней, Запорожский государственный медицинский университет, Украина.
Рябоконь Ю. Ю., д-р мед. наук, профессор каф. детских инфекционных болезней, Запорожский государственный медицинский университет, Украина.
Онищенко Н. В., д-р философии, ассистент каф. инфекционных болезней, Запорожский государственный медицинский университет, Украина.

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