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CHANGES IN CYTOKINE PROFILE IN HEPATITIS A: THE CONNECTION BETWEEN INFLAMMATION AND REGENERATION

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Abstract: Changes in TNF-α and HGF levels have been identified in hepatitis A, demonstrating a link between inflammation and regeneration. An increase in TNF-α indicates its role as an inflammatory mediator, while an increase in HGF reflects a response to hepatocyte destruction and stimulates their proliferation for liver repair. Higher HGF levels are associated with greater liver damage and the need for active repair.

Keywords: viral hepatitis, immune system, liver, cachexin, growth factor, cytokines, imbalance.

ГЕПАТИТ А ДА СИТОКИН ПРОФИЛИДАГИ ЎЗГАРИШЛАР: ЯЛЛИҒЛАНИШ ВА РЕГЕНЕРАЦИЯ ЎРТАСИДАГИ БОҒЛИҚЛИК

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Аннотация. Гепатит А да TNF-α ва HGF даражасидаги ўзгаришлар аниқланган, бу яллиғланиш ва регенератсия ўртасидаги боғлиқликни кўрсатади. Юқори TNF-α унинг яллиғланиш воситачиси ролини кўрсатади, HGF эса гепатоцитларнинг йўқ қилинишига жавобни акс эттиради ва уларнинг жигарни тиклаш учун кўпайишини рағбатлантиради. Юқори HGF даражалари жигарнинг кўпроқ шикастланиши ва фаол тикланиш зарурати билан боғлиқ.

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Калит сўзлар: вирусли гепатит, қон зардоби, жигар, кахексин, ўсиш омили, ситокинлар, мувозанат.

ИЗМЕНЕНИЯ ЦИТОКИНОВОГО ПРОФИЛЯ ПРИ ВГА: СВЯЗЬ ВОСПАЛЕНИЯ И РЕГЕНЕРАЦИИ

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Аннотация. Установлены изменения уровней TNF-α и HGF при ВГА, которые показывают связь между воспалением и регенерацией. Повышение TNF-α указывает на его роль как медиатора воспаления, а увеличение HGF отражает реакцию на разрушение гепатоцитов и стимулирует их пролиферацию для восстановления печени. Более высокие уровни HGF связаны с большими повреждениями печени и необходимостью активного восстановления.

Ключевые слова: вирусный гепатит, сыворотка, печень, кахексин, фактор роста, цитокины, дисбаланс.

Introduction. Hepatitis A virus (HAV) is a common infectious cause of acute hepatitis worldwide. According to the World Health Organization, infection rates in high-resource countries are low [1,6].

Clinical manifestations and outcomes of hepatitis A virus infection exhibit significant age-related differences. In adults, symptomatic acute hepatitis A occurs in more than 70% of cases, with 3% to 20% experiencing recurrent or prolonged hepatitis [1,7].

Given that the HAV virus is a non-cytopathic virus, this means that the virus itself does not cause hepatocyte damage; instead, it is the immune response that is responsible for the observed symptoms and liver damage [2]. The study of the cytokine profile in hepatitis A is highly relevant, since changes in cytokine levels can reflect the severity of the inflammatory process and the regenerative capacity of the liver [4]. Depending on the severity of the disease, the pattern and level of cytokine secretion vary significantly, making them valuable biomarkers for diagnosis, outcome prediction, and treatment optimization.

The aim of this study was to investigate serum levels of TNFα and HGF in different severities of HAV.

Material and methods of research. This study included 89 patients diagnosed with viral hepatitis A (HAV). All subjects were divided into groups based on the severity of their HAV infection: Group 1, with mild HAV infection, included 35 individuals; Group 2, with 33 individuals; and Group 3, with severe HAV infection, included 25 individuals. The control group consisted of 21 apparently healthy individuals. The entire sample was aged 18 to 24 years.

Immunological studies of the subjects were conducted in the Laboratory of Immunoregulation of the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan.

The concentration of tumor necrosis factor-alpha (TNFα) and hepatocyte growth factor (HGF) in the blood serum was determined by the enzyme-linked immunosorbent assay method using the test systems of JSC VECTOR-BEST (Russia) and Cusabio Biotech (China) in accordance with the manufacturer's recommendations.

Statistical processing of the obtained data was performed using the Statistica 6.0 computer program. The data were statistically processed using standard approaches, the results are presented as the sample mean (M) and standard error of the mean (m); the median (Me), characterizing the central tendency, and the upper and lower quartiles characterizing the spread of indicator values in 50% of respondents (Q1-Q3), where Q1 is the 25% percentile, Me is the 50% percentile, and Q3 is the 75% percentile. The significance of differences in the mean values (p) of the compared indicators was assessed using the Student's t-test.

Results and discussion. Table 1 shows changes in serum levels of TNF-α and HGF in patients with HAV of varying severity compared to the control group of practically healthy people.

Table 1.

Serum content of the studied markers in the examined groups before treatment

Indicator	M±m, pg/ml	Me [Q1; Q3]	*P-value*
Control group, n=21			
TNFα	20,60±1,23	19,74 [17,15; 24,74]	-
HGF	259,67±22,20	232,31 [221,92;	-
Group 1 (light form of VGA), n=35			
TNFα	48,93±1,45	49,29 [41,50; 57,88]	*p<0,001*
HGF	450,32±20,59	468,31	*p<0,001*
Group 2 (VGA medium heavy form), n=33			
TNFα	64,00±2,21	66,39 [52,31; 73,61]	*p<0,001*
HGF	555,56±22,59	574,28 [474,28;	*p<0,001*
Group 3 (VGA heavy form), n=25			
TNFα	97,59±3,11	97,60 [85,30;	*p<0,001*
HGF	563,04±23,78	589,360[491,15;	*p<0,001*

*Note: * - significant compared to control group data. Me – median, Q1 (percentile) – 25%, Q3 (percentile) – 75%.*

Tumor necrosis factor alpha (TNF-α) is a key proinflammatory cytokine produced primarily by macrophages, T lymphocytes, and neutrophils. It regulates the inflammatory response by recruiting immune cells to sites of infection, increases vascular permeability, and stimulates other cytokines. TNF-α also initiates apoptosis, controlling cell growth and eliminating damaged cells [3].

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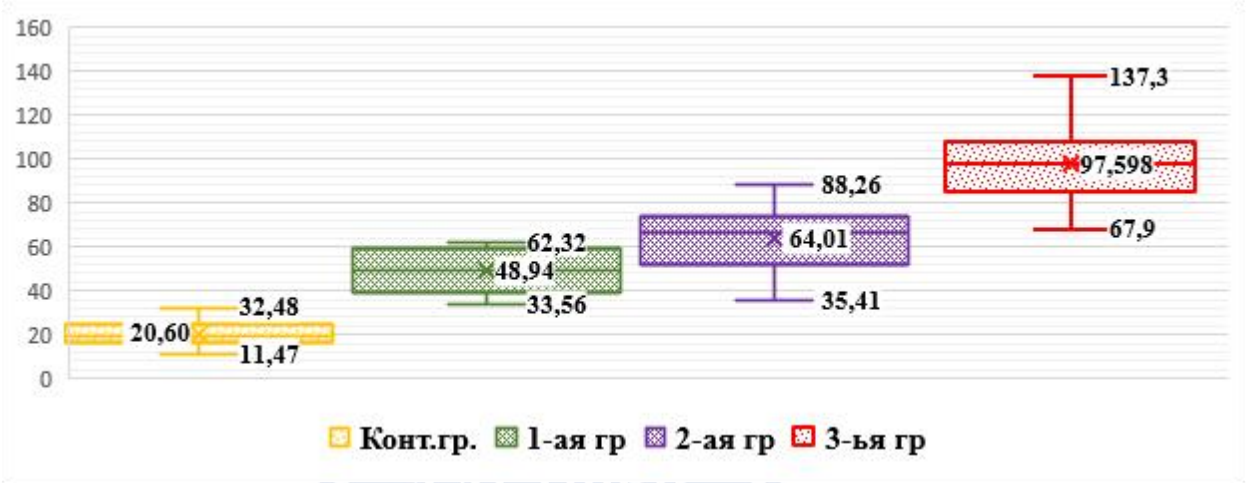

Fig. 1. Serum TNF-α levels in groups of patients with varying severity of viral hepatitis before treatment.

Analysis of serum levels revealed that in the 1st group of patients with mild hepatitis A, the TNF-α level increased to an average of 48.93 ± 1.45 pg/ml, which is more than 2.4 times higher than in the control group 20.60 ± 1.23 pg/ml ($p<0.001$), the median value (Me) of TNF-α also increased significantly to 49.29 pg/ml, which indicates a pronounced inflammatory process even with a mild degree of severity of hepatitis A. In the 2nd group with moderate hepatitis A, the TNF-α level increased even more significantly - to 64.00 ± 2.21 pg/ml, which is 3.1 times higher than the control values ($p<0.001$), Me was 66.39 pg/ml, which indicates the progression of the inflammatory response. The most pronounced increase in TNF-α was observed in the 3rd group of patients with severe HAV, where its level reached 97.59 ± 3.11 pg/ml, which is 4.7 times higher than the control group level of 20.60 ± 1.23 pg/ml ($p < 0.001$). Such a sharp increase is associated with an active systemic inflammatory response characteristic of severe forms of infection (Fig. 1).

Hepatocyte growth factor (HGF) is a key cytokine activated in response to tissue damage and promoting liver cell regeneration. The primary producers of HGF are mesenchymal cells, including fibroblasts, stromal cells, endothelium, and macrophages [4]. In the liver, HGF is synthesized by stellate cells and is activated upon injury, stimulating organ regeneration. HGF supports hepatocyte division and survival, stimulates angiogenesis and modulates inflammation, preventing excessive tissue damage and reducing the risk of fibrosis [5].

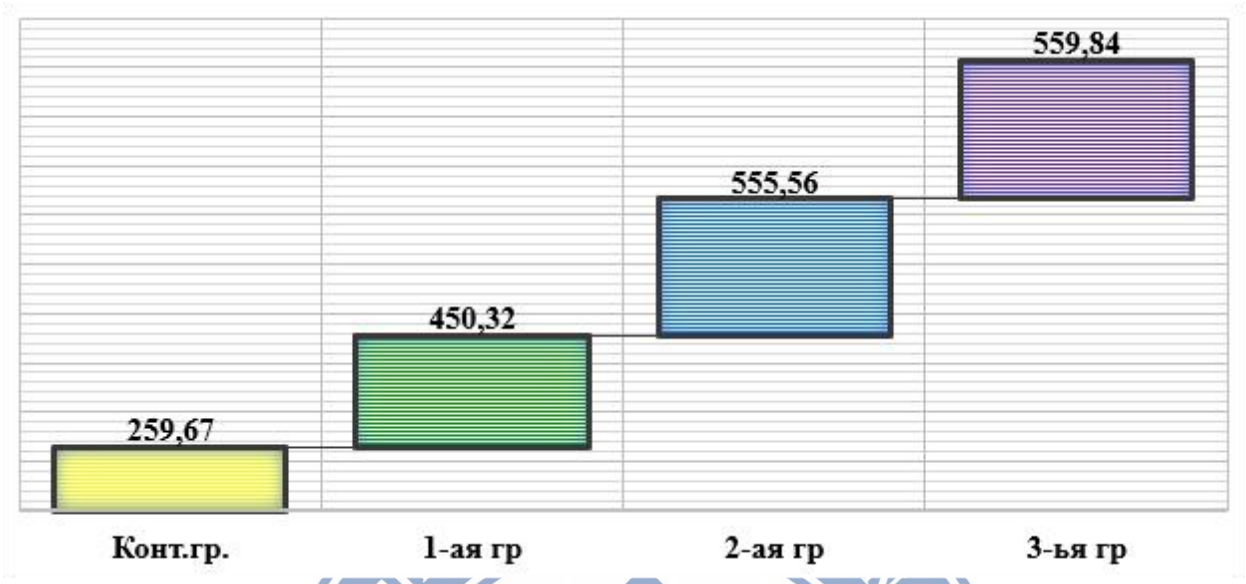

Fig. 2. Serum HGF levels in groups of patients with varying severity of HAV before treatment.

Figure 2 shows serum HGF levels in patients with varying degrees of HAV severity before treatment, compared with the control group. In healthy individuals in the control group, HGF levels averaged 259.67±22.20 pg/ml, with a median of 232.31 pg/ml and an individual range of 131.72 pg/ml to 449.17 pg/ml. Determination of serum levels revealed that in patients with mild HAV, the HGF level was significantly elevated: the average level was 450.32±20.59 pg/ml, which is 1.73 times compared to the control group ($p<0.001$), Me – 468.31 pg/ml, in the range from 204.84 pg/ml to 635.87 pg/ml. This increase in HGF levels may be associated with the activation of liver regeneration processes in response to virus-induced tissue damage, which is consistent with literature data on the role of HGF in stimulating liver cell regeneration.

In the group with moderate hepatitis A, the HGF level continued to increase and amounted to 555.56±22.59 pg/ml (median 574.28 pg/ml), which is 2.14 times higher ($p<0.001$) than in the control group, with minimum values of 310.39 pg/ml and maximum values of 727.21 pg/ml. Such an increase may indicate more severe liver damage, requiring enhanced activation of regenerative and compensatory mechanisms.

In patients with severe HAV, the average HGF level was 563.04±23.78 pg/ml (median 589.36 pg/ml) ($p<0.001$), with a range from 327.21 pg/ml to 777.21 pg/ml. Compared with the control group, this increase was approximately 2.17 times (Fig. 2).

The lack of significant difference in HGF levels in patients with moderate and severe HAV before treatment is related to the overall inflammatory response and regenerative liver function. In both cases, HGF increases in response to hepatocyte damage to stimulate liver repair. However, in severe HAV, further growth of HGF may be limited due to depletion of liver reserves and inflammation exceeding regenerative capacity, which inhibits the increase in HGF levels.

Thus, these changes in TNF-α and HGF demonstrate a relationship between the degree of inflammation and regeneration in the context of HAV. These results suggest that the increased TNF-α levels in HAV are due to its key role as an inflammatory mediator. An increase in HGF reflects the body's response to hepatocyte destruction caused by inflammation and viral damage. During liver regeneration, HGF stimulates hepatocyte proliferation, which is essential for the

restoration of organ function. As the disease progresses in severity, increased HGF levels are associated with greater liver tissue damage, requiring more active repair.

Conclusion

1. It has been established that the level of TNF-α increases with increasing severity of HAV, which reflects an increase in the inflammatory response, since TNF-α is a key pro-inflammatory cytokine that activates immune cells and increases inflammation.
2. It was found that the level of HGF also increases in HAV, which indicates the activation of regenerative processes in response to liver tissue damage. However, in severe cases, further growth of HGF is limited, which is associated with the possible depletion of the liver's regenerative reserves.
3. Elevated levels of TNF-α and HGF indicate a relationship between the inflammatory and regenerative responses in HAV, which can serve as a diagnostic and prognostic marker of the severity of the course and restoration of liver function.

References:

1. Clinical guidelines – Acute hepatitis A (HA) in adults – 2021-2022-2023 (10.02.2022) – p. 34

2. Novak KE, Bushmanova AD Epidemiological situation of viral hepatitis A in St. Petersburg. Medicine: Theory and Practice. 2019. Vol. 4. N S. pp. 389-390.

3. Immunology: structure and functions of the immune system. study guide / R.M. Khaitov. – Moscow: GEOTAR-Media, 2013 – 230 p.

4. Lanford RE, Walker CM, Lemon SM. The Chimpanzee Model of Viral Hepatitis: Advances in Understanding the Immune Response and Treatment of Viral Hepatitis. ILAR J. 2017 Dec 01;58(2):172-189.

5. Misumi I, Mitchell JE, Lund MM, Cullen JM, Lemon SM, Whitmire JK. T cells protect against hepatitis A virus infection and limit infection-induced liver injury. J Hepatol. 2021 Dec;75(6):1323-1334.

6. Odenwald MA, Paul S. Viral hepatitis: Past, present, and future. World J Gastroenterol. 2022 Apr 14;28(14):1405-1429.

7. Shin EC, Jeong SH. Natural History, Clinical Manifestations, and Pathogenesis of Hepatitis A. Cold Spring Harb Perspect Med. 2018 Sep 04;8(9).