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THE INTERRELATIONSHIP BETWEEN CHANGES IN IMMUNE AND BIOCHEMICAL INDICATORS IN AUTOIMMUNE LIVER DISEASE

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ABSTRACT

Significant hypergammaglobulinemia and the presence of many autoantibodies in the blood are symptoms of autoimmune hepatitis, a chronic liver illness with an unclear etiology that is characterized by periportal or more widespread inflammation. Current theories about the pathophysiology of AH include the interplay of genetic predisposition, immunological tolerance abnormalities, and environmental variables. The liver develops progressive non-inflammatory and fibrotic alterations as a result of this interaction, which triggers T-cell immune responses against hepatocyte antigens. With an annual incidence of 0.1–1.9 cases per 100,000 and a frequency of 3–17 instances per 100,000 in both Europe and the US, AH is regarded as a rather uncommon disease. Therefore, it is estimated that there are between 10,000 and 20,000 of these patients in the Russian Federation.

Introduction

Autoimmune hepatitis occurs when the immune system begins attacking the liver tissue. In this situation, the immune system reacts to outside agents like viruses; however, these responses are more commonly seen in people who have a genetic tendency towards them. Type 2 autoimmune hepatitis is a particular condition where molecular mimicry occurs, meaning that molecules found in viruses or bacteria look like those in the human body. Consequently, the body generates antibodies that attack its own liver microsomes, specifically those associated with

liver/kidney type 1 microsomes. These antibodies focus on the liver enzyme known as cytochrome P450 2D6 (CYP2D6). Therefore, type 2 autoimmune hepatitis arises through a mechanism of molecular mimicry, which activates immune responses against liver enzymes [9].

Brazilian scientists have studied the occurrence of autoimmune hepatitis (AIH) in patients with chronic hepatitis B infection. In the study, liver biopsies from 1,759 patients were taken, and 92 were confirmed to have AIH. Moreover, among individuals suffering from chronic hepatitis C infection, the outcomes noted were as follows: 66% of these individuals tested positive for SMA (smooth muscle antibodies), 41% had LKM (liver kidney microsomal) antibodies, and a certain percentage of cases showed a positive ANA (antinuclear antibody). These results suggest that hepatitis viruses can coexist with autoimmune hepatitis. This research points to the simultaneous presence of hepatitis viruses and autoimmune hepatitis, meaning that viruses might stimulate autoimmune reactions and lead to hepatitis. The main therapeutic agents used in treating AIH are corticosteroids and azathioprine, which help normalize liver enzymes and immunoglobulin G (IgG) levels, leading to remission (the period when the disease enters its inactive phase) [2].

Furthermore, 40% of patients with AIH have a family history of autoimmune diseases, which supports the genetic inheritance of autoimmune conditions. This suggests a genetic basis for the disease and indicates the potential for familial transmission. Although AIH and other autoimmune diseases are related to genetic inheritance, they do not follow Mendelian inheritance. In Mendelian inheritance, diseases are passed through genes located on specific chromosomes, whereas autoimmune diseases are often influenced by multiple genetic factors and environmental factors [10].

Thus, while individuals with a family history of autoimmune diseases may carry genetic risk factors, environmental factors (such as infections, stress, diet, and other factors) also play a significant role. These factors can cause the immune system to react improperly, leading to the development of autoimmune diseases. Autoimmune hepatitis in children is primarily associated with genetic predisposition. The connection between human leukocyte antigens (HLA) and type 1 AIH was first identified 30 years ago [1].

In 1990, Donaldson and colleagues studied the impact of HLA in 96 patients with AIH and 14 patients who had undergone liver transplantation. In AIH patients, HLA-DR3 and HLA-DR4 antigens were found. AIH patients with the HLA DR3 antigen had a poor prognosis, with low treatment efficacy and a high need for liver transplantation [5].

ANA, SMA, anti-LKM1, anti-LC1, and antimitochondrial antibodies were first identified in tissue samples (kidney, liver, and stomach) using human IgG conjugates as detection reagents [7].

The main part. Through the Liver-9-Line immunoblot testing technique, we examined 9 different antibodies along with liver biochemical indicators found in chronic autoimmune liver disorders.

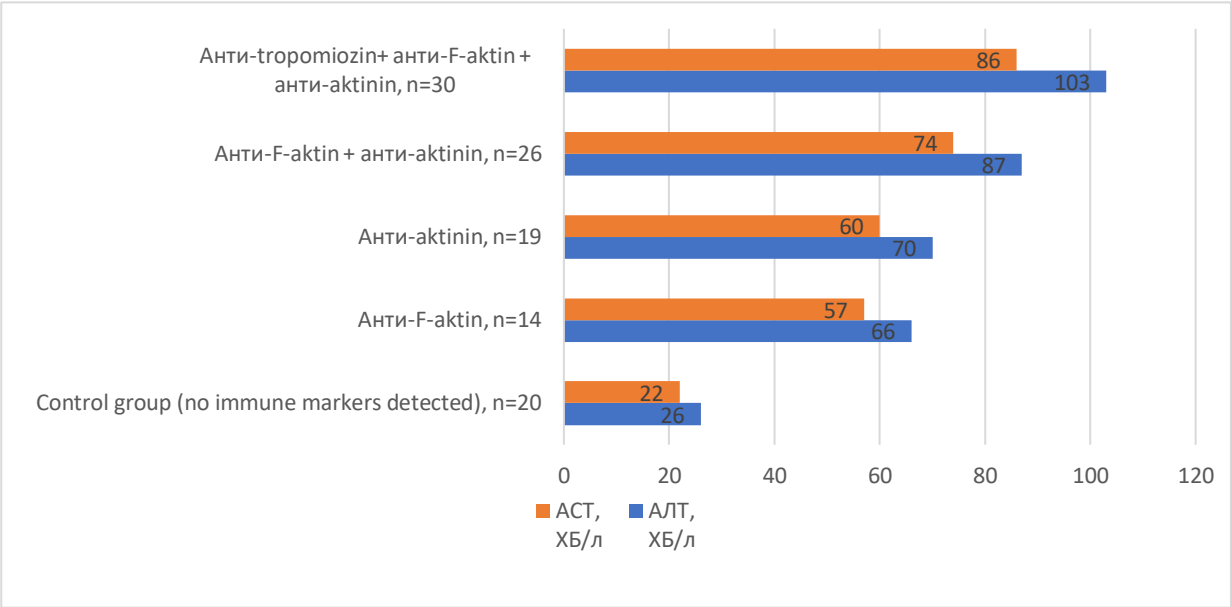


Diagram 1. Autoimmune and liver cell destruction indicators in type 1 autoimmune hepatitis and autoimmune liver scarring

In the initial group, which consisted of 89 patients with type 1 autoimmune hepatitis, along with the third group suffering from type 1 autoimmune liver cirrhosis, it was found that 63.0% tested positive for the anti-F-actin and anti-actinin markers. Additionally, 15.7% of those patients had solely anti-F-actin, while 21.3% had only positive results for anti-actinin. Anti-tropomyosin was positive in a total of 30 patients with type 1 autoimmune hepatitis and autoimmune liver cirrhosis, and all these patients also tested positive for anti-F-actin and anti-actinin markers in the ASMA group. The results of studying alanine aminotransferase, aspartate aminotransferase, and their ratio in these patients are presented in Diagram 1.

From Diagram 1, we can observe that in 14 patients with anti-F-actin, alanine aminotransferase (ALT) was 66±12 U/L ($p<0.01$), aspartate aminotransferase (AST) was 57±8 U/L ($p<0.01$), and the Ritis ratio was 1.16 ± 0.08. Similar changes were observed in 19 patients with anti-actinin: ALT was 70±16 U/L ($p<0.01$), AST was 60±9 U/L ($p<0.01$), and the Ritis ratio was 1.17 ± 0.09.

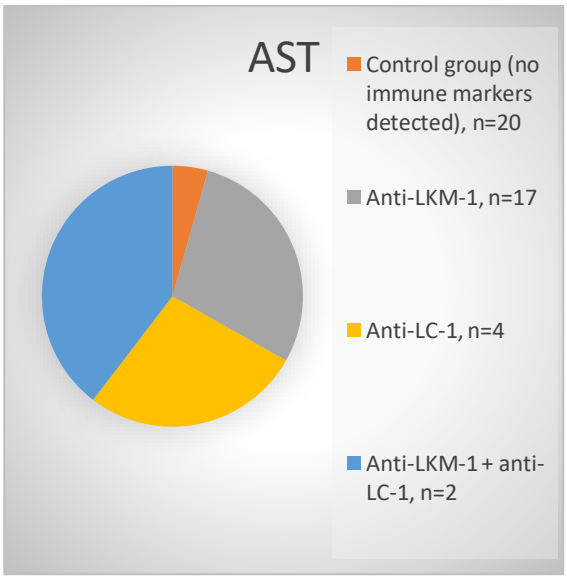
The examination results showed that in patients with multiple types of antibodies

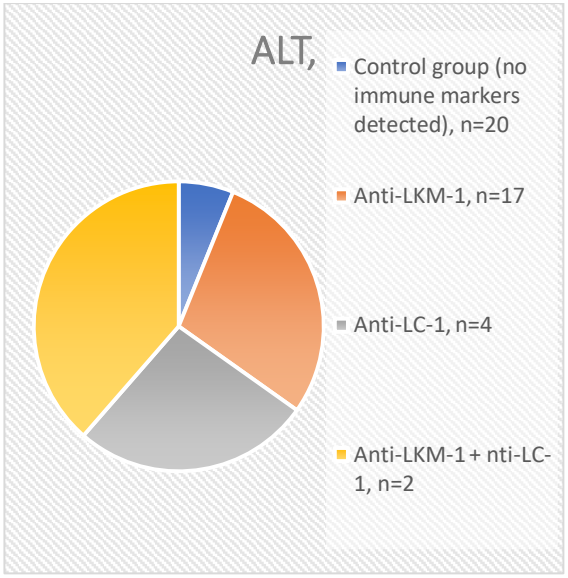
detected, these indicators changed more significantly. Among 26 patients with both anti-F-actin and anti-actinin, ALT was 87±18 U/L ($p<0.001$), AST was 74±11 U/L ($p<0.001$), and the Ritis ratio was 1.17 ± 0.10. In 30 patients with anti-tropomyosin, anti-F-actin, and anti-actinin, ALT was 103±28 U/L ($p<0.001$), AST was 86±13 U/L ($p<0.001$), and the Ritis ratio was 1.20 ± 0.14.

In the second group, among 23 patients with type 2 autoimmune hepatitis and the fourth group with autoimmune liver cirrhosis, 73.9% of patients had anti-LKM-1, 17.4% had anti-LC-1, and 8.7% had both anti-LKM-1 and anti-LC-1 antibodies.

In 17 patients with anti-LKM-1, ALT was 122 ± 22 U/L ($p<0.001$), AST was 144 ± 28 U/L ($p<0.001$), and the Ritis ratio was 0.85 ± 0.05 ($p<0.001$). Additionally, in 4 patients with anti-LC-1, ALT was 113 ± 19 U/L ($p<0.001$), AST was 136 ± 25 U/L ($p<0.001$), and the Ritis ratio was 0.83 ± 0.05 ($p<0.001$) (Diagram 2).

Diagram 2: Autoimmune and Liver Cytolysis Markers in Type 2 Autoimmune Hepatitis and Autoimmune Liver Cirrhosis



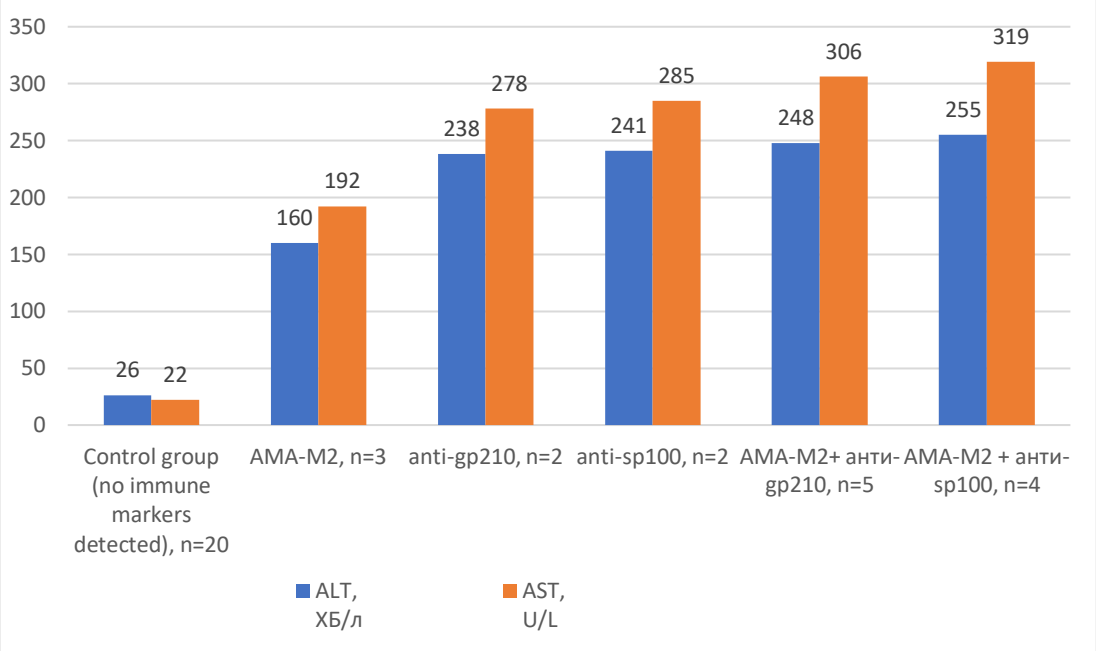


From Diagram 2, it is evident that in 2 patients with both anti-LKM-1 and anti-LC-1, these indicators increased sharply: alanine aminotransferase (ALT) was 164 ± 35 U/L ($p<0.001$), aspartate aminotransferase (AST) was 198 ± 41 U/L ($p<0.001$), and the Ritis ratio was 0.83 ± 0.04 ($p<0.001$).

In the fifth group, among 12 patients diagnosed with primary biliary cholangitis (AMA-M2 positive), 31.2% had anti-gp210, 25.0% had anti-sp100 (anti-nuclear antibodies), while in AMA-M2 negative patients, 12.5% had anti-gp210 and 12.5% had anti-sp100. In these patients, ALT and especially AST levels increased sharply, and the Ritis ratio decreased significantly.

In three AMA-M2 positive patients: ALT was 160 ± 42 U/L ($p<0.01$), AST was 192 ± 28 U/L ($p<0.001$), and the Ritis ratio was 0.83 ± 0.06 ($p<0.001$). Similar trends were observed in individual patients with anti-gp210 and anti-sp100: ALT was 238 ± 49 U/L ($p<0.001$) and 241 ± 22 U/L ($p<0.001$), AST was 278 ± 28 U/L ($p<0.001$) and 285 ± 28 U/L ($p<0.001$), and the Ritis ratio was 0.86 ± 0.05 ($p<0.001$) and 0.85 ± 0.06 ($p<0.001$), respectively (Diagram 3).

Diagram 3. Autoimmune and Liver Cytolysis Markers in Primary Biliary Cholangitis



In 5 patients with AMA-M2 and anti-gp210, and 4 patients with AMA-M2 and anti-sp100, these indicators were even higher: alanine aminotransferase (ALT) was 248 ± 19 U/L ($p<0.001$) and 255 ± 35 U/L ($p<0.001$), aspartate aminotransferase (AST) was 306 ± 25 U/L ($p<0.001$) and 319 ± 41 U/L ($p<0.001$), and the Ritis ratio was 0.81 ± 0.05 ($p<0.001$) and 0.80 ± 0.07 ($p<0.001$), respectively.

Conclusion

In chronic autoimmune liver diseases, the study of antibodies and liver biochemical markers using the Liver-9-Line immunoblot analysis revealed that in patients with autoimmune hepatitis and autoimmune liver cirrhosis, anti-F-actin, anti-actinin, and anti-tropomyosin antibodies were associated with a 4-fold increase in ALT and a 3.9-fold increase in AST compared to the control group. In patients with anti-LKM-1 and anti-LC-1 antibodies, ALT increased up to 6.3-fold and AST up to 9.0-fold. In AMA-M2 positive primary biliary cholangitis (PBC) patients, ALT and AST levels increased up to 10-fold.

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