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THE ROLE OF LABORATORY INVESTIGATIONS IN THE EARLY DIAGNOSIS OF AUTOIMMUNE HEPATITIS

Abstract

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease caused by an immune-mediated attack on hepatocytes, which, if diagnosed late, can progress to cirrhosis and liver failure. Because the clinical manifestations of AIH are often nonspecific, early diagnosis relies primarily on laboratory investigations. This article comprehensively analyzes the diagnostic value of biochemical (aminotransferases, bilirubin, liver enzymes), immunological (immunoglobulin G, autoantibodies – ANA, ASMA, LKM1, SLA), and morphological (liver biopsy) markers in the early detection of AIH.

The analysis shows that a combined evaluation of aminotransferase levels, elevated IgG concentration, and positive autoantibody profiles increases the likelihood of early diagnosis up to 90%. In addition, the paper discusses differential diagnosis from viral and toxic hepatitis, the logical sequence of laboratory testing, and the importance of dynamic monitoring. Based on contemporary diagnostic algorithms and international clinical recommendations, a strategy for early detection of AIH adapted to the healthcare context of Uzbekistan is proposed.

Keywords: autoimmune hepatitis; laboratory diagnosis; early detection; aminotransferases; immunoglobulin G (IgG); autoantibodies (ANA, ASMA, LKM-1, SLA); liver biopsy; liver enzymes; immunological markers; clinical diagnostic strategy.

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РОЛЬ ЛАБОРАТОРНЫХ ИССЛЕДОВАНИЙ В РАННЕЙ ДИАГНОСТИКЕ АУТОИММУННОГО ГЕПАТИТА

Аннотация

Аутоиммунный гепатит (АИГ) — это хроническое воспалительное заболевание печени, обусловленное иммунной атакой на собственные гепатоциты, что при поздней диагностике может привести к развитию цирроза и печёночной недостаточности. Клинические проявления АИГ, как правило, неспецифичны, поэтому ранняя диагностика основывается преимущественно на лабораторных исследованиях. В статье подробно рассмотрена роль биохимических (аминотрансферазы, билирубин, ферменты печени), иммунологических (иммуноглобулин G, аутоантитела — ANA, ASMA, LKM1, SLA) и морфологических (биопсия печени) показателей в раннем выявлении заболевания.

Результаты анализа показывают, что сочетанная оценка уровня аминотрансфераз, IgG и положительных аутоантител повышает вероятность раннего выявления АИГ до 90 %. Кроме того, рассмотрены вопросы дифференциальной диагностики с вирусными и токсическими гепатитами, последовательность лабораторных тестов и практическое значение динамического мониторинга. На основе современных диагностических алгоритмов и клинических рекомендаций предложена стратегия раннего выявления АИГ, адаптированная к условиям системы здравоохранения Узбекистана.

Ключевые слова: аутоиммунный гепатит; лабораторная диагностика; ранняя диагностика; аминотрансферазы; иммуноглобулин G (IgG); аутоантитела (ANA, ASMA, LKM-1, SLA); биопсия печени; ферменты печени; иммунологические маркеры; клиническая стратегия диагностики.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by an immune-mediated attack on hepatocytes; its etiology has not been fully elucidated. AIH occurs more frequently in women and exhibits heterogeneous clinical presentations—ranging from asymptomatic forms to severe manifestations resembling acute hepatitis.

According to the American Association for the Study of Liver Diseases (AASLD) [8], AIH accounts for 5–10% of chronic liver diseases. If not recognized in a timely manner, it can lead to early fibrosis, subsequent cirrhosis, and liver failure. Recent reports from the Biotechnology Center emphasize the combined roles of genetic susceptibility (HLA-DR3, DR4), viral infections, hormones, environmental factors, and disturbed immune regulation in AIH pathogenesis.

At early stages, symptoms are usually nonspecific—fatigue, loss of appetite, dyspeptic complaints, and occasionally mild jaundice of the skin and sclerae. Consequently, AIH is frequently misdiagnosed as viral, alcoholic, or drug-induced hepatitis. Analyses summarized in PMC [5] indicate that in 40% of patients with a delayed diagnosis, fibrosis–cirrhosis has already begun in liver tissue.

The cornerstone of early diagnosis is laboratory testing, which helps characterize the immune mechanism, activity of inflammation, and response to therapy. Laboratory studies are crucial not only for identifying AIH but also for differential diagnosis with other etiologies of liver disease.

Role of Laboratory Testing and Diagnostic Stages

Laboratory studies are central to AIH diagnosis. They determine the immunologic nature of disease, grade its activity, support differential diagnosis, and monitor treatment effectiveness. According to AASLD (2023), 60–70% of AIH cases are first detected through laboratory testing, with clinical symptoms recognized later. Thus, laboratory evaluation is the foundation for early detection and ongoing monitoring.

Biochemical Liver Tests

The first step is to assess hepatic enzyme activity. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are the most sensitive—but relatively nonspecific—markers of AIH. Their levels typically rise to 5–15 times the upper limit of normal, though at an early stage increases may be only 1.5–2 times. The Biotechnology Center's 2024 observations report elevated AST/ALT in 92% of AIH patients, while 8% remain within normal limits.

Elevated aminotransferases reflect hepatocellular necrosis but are not sufficient alone for diagnosis; therefore, additional tests are performed: total and direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), prothrombin time, and albumin. In AIH, ALP is often normal or only mildly elevated, which helps distinguish AIH from cholestatic disorders.

Immunoglobulins and Hypergammaglobulinemia

An increased level of immunoglobulin G (IgG) is characteristic of AIH. AASLD and EASL (2022) guidelines consider IgG > 1.1 × the upper limit of normal a diagnostic criterion. IgG elevation occurs in 90–95% of type 1 AIH and about 80% of type 2 AIH. Elevations in IgM or IgA typically suggest other liver diseases (e.g., primary biliary cholangitis or alcoholic hepatitis).

Measuring IgG is also useful for activity assessment and treatment monitoring: a decline in IgG during therapy with prednisolone or azathioprine can be an early sign of clinical improvement.

Serologic Testing for Autoantibodies

Serologic assays form the core immunologic component of AIH diagnosis and confirm an immune-mediated process:

- **ANA (antinuclear antibodies):** positive in ~80% of type 1 AIH.
- **ASMA (anti–smooth muscle antibodies):** positive in ~63%.
- **Anti-LKM-1 (liver–kidney microsomal antibodies):** typical of type 2 AIH, seen more often in children.
- **Anti-SLA/LP (soluble liver antigen/liver–pancreas antibodies):** the most specific markers (≈95–100% specificity).

However, the absence of these antibodies does not exclude AIH. Seronegative AIH (ANA-, ASMA-, LKM-) is seen in 10–15% of patients [9]; in such cases, the diagnosis is supported by elevated IgG and characteristic histology.

Histologic Examination and the Laboratory's Role

Definitive confirmation of AIH requires liver biopsy. Laboratory findings guide the decision to biopsy. Histology typically demonstrates lymphoplasmacytic infiltration, portal tract injury, and features of "interface hepatitis." Biopsy also helps assess disease severity and differentiate AIH from other etiologies (e.g., hepatitis B or C, steatohepatitis).

Differential-Diagnostic Laboratory Indicators

Laboratory work-ups help distinguish AIH from:

- **Viral hepatitides (HBV, HCV, HEV):** excluded by viral markers (e.g., HBsAg, anti-HCV).
- **Drug-induced liver injury:** supported by medication history and eosinophilia.
- **Metabolic diseases** (Wilson's disease, hemochromatosis): evaluated by ceruloplasmin, copper, ferritin, and transferrin saturation.
- **Alcoholic hepatitis:** suggested by elevated GGT and MCV with absence of autoantibodies.

Laboratory panels must always be interpreted alongside the clinical picture and history.

Steps of the Diagnostic Algorithm

Stage I — Identify patients with elevated liver enzymes (AST, ALT, bilirubin).

Stage II — Measure IgG and γ-globulins; if elevated, AIH becomes more likely.

Stage III — Test autoantibodies (ANA, ASMA, anti-LKM-1, anti-SLA).

Stage IV — Exclude viral, metabolic, and drug-related causes.

Stage V — Confirm by biopsy and histology.

When performed sequentially, diagnostic accuracy may reach up to 95% [3].

Importance of Laboratory Monitoring

Once AIH is diagnosed, laboratory tests are essential for follow-up. On therapy (prednisolone ± azathioprine), normalization of AST/ALT, decline in IgG, and decreasing autoantibody titers indicate remission; renewed elevations suggest relapse.

In addition, complete blood count, glucose, electrolytes, creatinine, leukocytes, and platelets should be monitored during treatment, as immunosuppressants—particularly azathioprine—can cause hematologic adverse effects.

Modern Laboratory Technologies

In recent years, molecular-biotechnology approaches have been adopted for AIH diagnostics:

- **Multiplex ELISA** platforms enable simultaneous detection of several autoantibodies.
- **Recombinant antigen systems** facilitate detection of anti-SLA, anti-LC1, and other markers.
- **Proteomics-based assays** are being explored for novel immune markers (e.g., CYP2D6, FTCD antigens).

According to the Biotechnology Center (2024), these technologies increase the sensitivity of early (subclinical) AIH detection by 15–20%.

Description of Early-Detection Laboratory Tests

Early recognition of AIH is clinically important because initial manifestations are often subtle or nonspecific. Laboratory testing functions as a "mirror" of the ongoing immune pathology, revealing abnormalities well before overt symptoms.

Aminotransferases (ALT and AST). Multiple studies (PMC, 2023) show that 80% of patients with early AIH have ALT/AST levels 1.5–3 × the upper limit of normal. Unlike viral or toxic hepatitis, AIH tends to produce moderate rather than abrupt spikes. A relatively mild yet persistent elevation can therefore be an early laboratory signal of autoimmunity. The **AST/ALT ratio** in AIH is generally near 1 or slightly below, contrasting with alcoholic hepatitis, where AST/ALT > 2 is common.

Immunoglobulin G (IgG). Driven by B-cell and plasma-cell hyperactivity, IgG rises early in AIH. The EASL (2022) guideline notes that an IgG increase of 1.1–1.5 × the upper limit of normal reflects disease activity—even when clinical signs are minimal. A selective rise in IgG (without concurrent increases in IgM/IgA) supports differentiation from PBC or alcoholic hepatitis. IgG monitoring also helps track response: normalization on corticosteroids signals early remission.

Autoantibody testing.

- **ANA:** the most sensitive marker for type 1 AIH; fluorescence patterns are often "speckled" or "homogeneous."
- **ASMA:** positive in ~60–70%; directed against actin filaments. Co-positivity with ANA increases diagnostic likelihood.
- **Anti-LKM-1:** typical for type 2 AIH, more frequent in children/adolescents.

- **Anti-SLA/LP:** highest specificity (95–100%); can confirm diagnosis when other tests are negative.

Liver function indices. In early AIH, total bilirubin, ALP, and GGT are usually normal or only mildly elevated—unlike cholestatic hepatitides. Albumin is typically preserved early and may decrease only in advanced disease due to impaired hepatic synthesis. This relative stability should not mislead clinicians: it often reflects a "quiet" early phase of AIH.

Concordance with histology and molecular tests. When ALT/AST and IgG are elevated and autoantibodies are present, biopsy demonstrating portal-zone lymphoplasmacytic infiltrates and interface hepatitis solidifies the diagnosis. Emerging multiplex ELISA and recombinant-antigen assays can detect multiple antibodies at once (ANA, ASMA, SLA, LKM-1), improving accuracy by 15–20% compared with classic single assays.

Combined testing—benchmark for diagnostic accuracy. No single assay definitively diagnoses AIH. A combination is most reliable. The following **triad** carries strong early diagnostic value:

1. ALT/AST above normal (≥ 1.5 × ULN)
2. Elevated IgG (≥ 1.1 × ULN)
3. At least one positive autoantibody (ANA, ASMA, LKM-1, or SLA)

When present, the probability of AIH is estimated at ~85–95%.

Diagnostic Strategy

Because AIH shares overlapping laboratory and clinical features with other hepatitides, a stepwise, integrated approach is required—clinical assessment, laboratory-immunologic testing, and histologic confirmation.

Clinical stage — triggers for suspicion Consider AIH in patients with unexplained transaminase elevation, especially when:

- ALT/AST are elevated without a clear cause;
- IgG or γ-globulins are above normal;

- there is coexisting autoimmunity (thyroiditis, rheumatoid arthritis, type 1 diabetes) with elevated liver enzymes;
- viral hepatitis markers (HBsAg, anti-HCV) are negative.

Laboratory-immunologic stage — the main diagnostic engine

- **Transaminases:** in viral hepatitis, rises may be abrupt (10–20 × ULN), whereas in AIH they are often moderate (3–10 × ULN) or even mild.
- **Immunoglobulins:** IgG 1.1–1.5 × ULN is an important indicator of active immune inflammation; lack of IgM/IgA elevation increases specificity for AIH.
- **Autoantibodies:** ANA/ASMA suggest type 1 AIH; anti-LKM-1 suggests type 2; anti-SLA/LP has the highest specificity. Seronegativity (10–15%) does not exclude AIH—elevated IgG and biopsy remain decisive.
- **Exclude viral hepatitis:** HBsAg, anti-HCV, HCV-RNA, HBV-DNA are mandatory.
- **Exclude metabolic/drug causes:** ceruloplasmin and 24-h urinary copper (Wilson's), ferritin and transferrin saturation (hemochromatosis), and a careful drug history.

Histologic stage — final confirmation

Typical features:

- lymphoplasmacytic infiltration in portal tracts;
- **interface hepatitis** (inflammation extending from portal areas into parenchyma);
- **rosette formation** of hepatocytes;
- fibrosis or early cirrhotic change.

Combined interpretation of laboratory and histologic data yields diagnostic accuracy of 92–95% [9].

Stepwise algorithm

1. Baseline labs: AST/ALT, bilirubin, ALP, GGT.
2. Immunologic screening: IgG and γ-globulins.

3. Autoantibodies: ANA, ASMA, anti-LKM-1, anti-SLA.
4. Viral markers: HBV, HCV, HAV, HEV.
5. Metabolic causes: ceruloplasmin, ferritin, transferrin saturation; drug history.
6. Biopsy for confirmation and grading of activity.
7. Scoring (IAIHG): scores > 6 strongly support AIH.

Integrated assessment

- Elevated IgG, ANA/ASMA positive, viral markers negative → high likelihood of AIH.
- Elevated ALT/AST with normal IgG and negative ANA → consider drug-induced injury or steatohepatitis.
- Mildly elevated ALT/AST, slightly elevated IgG, autoantibodies negative → consider seronegative AIH.

According to the Biotechnology Center (2024), applying this integrated approach led to clinical remission within 6 months in 85% of patients diagnosed early.

Goal and impact early diagnosis improves prognosis: with timely immunosuppression (prednisolone, azathioprine), complete remission is achieved in over 80% of patients, whereas late-diagnosed cases with established fibrosis achieve remission in only 40–50%. Therefore, primary care algorithms for elevated aminotransferases should routinely evaluate an autoimmune component.

Practical Recommendations early detection of AIH in clinical practice is vital. Modern laboratory approaches reveal immune-pathologic processes early, improving outcomes and reducing risks of cirrhosis and liver failure. Key recommendations [12]:

- **Do not delay screening** in suspicious cases. In any patient with elevated ALT/AST— even if asymptomatic—consider AIH. After excluding viral and toxic causes, measure IgG and test for autoantibodies (ANA, ASMA,

anti-LKM-1, anti-SLA). AASLD (2023) notes this strategy increases early diagnosis by 35–40%.

- **Interpret tests in combination.** No single result suffices. For example, isolated transaminase elevations with normal IgG suggest drug-induced injury, fatty liver, or metabolic disease; positive IgG and autoantibodies with negative viral markers strongly suggest AIH.
- **Monitor IgG and autoantibody dynamics.** Every 3–6 months check AST, ALT, bilirubin, IgG, and antibody titers (ANA, ASMA, SLA). Declining IgG and normalized transaminases indicate effective therapy; renewed rises suggest relapse.
- **Implement a stepwise exclusion algorithm** for viral and metabolic hepatitides to reduce misclassification and optimize resource use [11].
- **Refer to hepatology/immunology** when transaminases remain elevated with negative viral markers, especially in patients with coexisting autoimmune diseases.
- **Pre-treatment work-up** before immunosuppression: CBC, renal and hepatic function (creatinine, ALT, AST, albumin, PT/INR), glucose and lipid profile, HBV-DNA/HCV-RNA, and pregnancy testing (for women).
- **Adopt a standard "AIH screening panel"** in laboratories (ALT, AST, bilirubin; IgG/IgM/IgA; ANA, ASMA, anti-LKM-1, anti-SLA) as recommended by the Biotechnology Center (2024).
- **Use a pre-biopsy laboratory "triad":** (1) elevated ALT/AST, (2) elevated IgG, (3) at least one positive autoantibody. If any two are present, proceed to biopsy.
- **Establish structured monitoring** during immunosuppression (prednisolone, methylprednisolone, azathioprine, mycophenolate mofetil): monthly AST/ALT, IgG, glucose, lipids, blood counts; reassess ANA/ASMA every 6 months; adjust therapy if laboratory parameters worsen.

- **Expand early-diagnosis programs** within primary care in Uzbekistan: annual ALT/AST, IgG, and autoantibody testing for at-risk patients; prompt referral to hepatology; targeted training for laboratory personnel.

Conclusion

Early identification of autoimmune hepatitis requires comprehensive and purposeful use of laboratory testing. Elevations in aminotransferases, increased IgG, and positive autoantibodies are key indicators, but none is pathognomonic alone; clinical context and differential diagnosis are essential. Early diagnosis and scheduled monitoring improve outcomes. Within Uzbekistan's healthcare setting, incorporating autoimmune markers into standard liver disease screening and considering AIH among under-recognized etiologies will enhance early detection and reduce progression to cirrhosis.

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