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Acute hepatitis B: Diagnostic approach based on clinical and serological findings

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Abstract

Accurate diagnosis of acute hepatitis B requires a proper correlation between clinical findings and the interpretation of serological profiles. Understanding the sequence of appearance and disappearance of viral markers allows for the early identification of the infection, guides clinical management, and prevents disease complications and transmission.

Keywords: Acute hepatitis B; Hepatitis B virus; Serological diagnosis; IgM anti-HBc; HBsAg; Viral markers

1. Introduction

Hepatitis B virus (HBV) infection remains one of the leading causes of liver disease worldwide. Approximately 296 million people were living with chronic HBV infection in 2019, and nearly 820,000 deaths associated with its complications—primarily cirrhosis and hepatocellular carcinoma—were recorded. Despite the availability of highly effective vaccines for more than four decades, hepatitis B continues to pose a major challenge to healthcare systems due to persistent vertical transmission, migration from endemic regions, and a high proportion of individuals lacking a timely diagnosis (1).

Viral hepatitides constitute one of the primary causes of infectious morbidity and mortality worldwide, causing approximately 1.4 million annual deaths. More than 90% of these deaths are related to the consequences of chronic HBV and HCV infections, particularly liver cirrhosis and hepatocellular carcinoma (2). These data demonstrate that, although clinical interest often focuses on the chronic forms of the disease, early recognition of acute infection remains critical to interrupting the chain of transmission and preventing progression toward chronic carrier states.

The geographical distribution of hepatitis B is heterogeneous. High-endemicity regions, such as Southeast Asia and much of Sub-Saharan Africa, present prevalences exceeding 6%, whereas North America and Western Europe are considered low-endemicity areas. However, migratory movements have significantly modified global epidemiology, favoring the persistence of cases in countries traditionally deemed low-risk (3).

2. Natural History of Acute Hepatitis B

The clinical evolution of acute HBV infection depends fundamentally on the age at viral acquisition and the host's immune status. Perinatal transmission is associated with chronicity rates close to 95%, whereas infection acquired during adulthood carries a probability of chronicity below 5% in immunocompetent individuals (3).

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The incubation period of acute hepatitis B typically ranges between a few weeks and 6 months, with a general average of 60 to 90 days. Nearly two-thirds of adult patients who acquire the infection acutely experience an asymptomatic or subclinical course that usually goes unnoticed (6).

Most cases of acute hepatitis B run an asymptomatic course or present with non-specific clinical manifestations. It is estimated that approximately two-thirds of patients do not exhibit evident symptoms, which hinders early diagnosis and promotes inadvertent transmission. When the disease is clinically manifest, it usually presents with constitutional symptoms such as fever, asthenia, anorexia, nausea, general malaise, and right upper quadrant pain, followed by jaundice, choluria, and acholia in more advanced cases (3).

Progression toward acute liver failure is uncommon, observed in about 1% of patients, although it constitutes a potentially life-threatening complication. The authors highlight that hepatitis B is responsible for approximately 7% of acute liver failure cases reported in various clinical series (3).

3. Virological and Pathophysiological Principles Relevant to Diagnosis

HBV belongs to the *Hepadnaviridae* family and possesses a partially double-stranded DNA genome with a complex replicative strategy that includes a reverse transcription phase. The persistence of covalently closed circular DNA (cccDNA) in hepatocytes constitutes the primary mechanism responsible for chronicity and the potential for viral reactivation years after the apparent clinical resolution of the infection (1).

From a pathophysiological standpoint, the liver damage associated with hepatitis B is not primarily caused by a direct cytopathic effect of the virus, but rather by the host's immune response against infected hepatocytes. The intensity of this response determines both the severity of the acute hepatitis and the probability of spontaneous viral clearance. Patients who develop a vigorous immune response typically achieve infection resolution and the appearance of protective antibodies against the surface antigen (anti-HBs), whereas a deficient response favors viral persistence (1).

4. Serological Diagnosis of Acute Hepatitis B

The diagnosis of acute hepatitis B is based on the proper interpretation of serological markers. HBsAg is the first detectable marker following infection and represents evidence of active infection. However, the most critical serological marker to confirm a recent acute infection is the IgM antibody against the core antigen (IgM anti-HBc), especially during the so-called window period—a stage in which HBsAg has disappeared and anti-HBs antibodies are not yet detectable (1).

The differential diagnosis between acute hepatitis B and an exacerbation of chronic hepatitis B can be complex, particularly in patients unaware of their prior serological status. In this context, the quantification of IgM anti-HBc becomes particularly relevant, given that its titers are usually significantly higher during primary acute infection (3).

It is recommended to complement the serological evaluation with the determination of HBeAg, anti-HBe, and HBV-DNA. These markers allow for establishing the degree of viral replication, assessing infectivity potential, and guiding clinical follow-up. Likewise, the measurement of aminotransferases, especially ALT, remains a fundamental tool for estimating hepatic inflammatory activity (4).

5. Interpretation of Serological Profiles

The integrated interpretation of serological markers allows for the establishment of different phases of the infection. The simultaneous presence of HBsAg and IgM anti-HBc is highly suggestive of acute hepatitis B. Subsequently, during infection resolution, HBsAg disappears and anti-HBs appears, which is considered a marker of protective immunity.

During the window period, the sole serological evidence of recent infection may be positivity for IgM anti-HBc. This finding holds critical diagnostic importance, as it prevents the misclassification of patients as susceptible or uninfected. Various authors agree that recognizing this phase constitutes one of the main diagnostic challenges in clinical practice (1,3,4).

HBV-DNA quantification adds complementary information regarding the replicative activity of the virus. Although it is not indispensable for confirming acute infection, it is particularly useful in patients with an atypical course, suspected fulminant hepatitis, or the need to evaluate antiviral treatment (1,4).

6. Diagnostic Approach Based on Serological Markers

Upon clinical suspicion of an acute hepatitis B virus (HBV) infection, confirmatory diagnosis requires the precise evaluation and interpretation of a panel of serum serological and virological markers:

Hepatitis B Surface Antigen (HBsAg): It is detectable in serum between 2 and 10 weeks post-exposure, appearing early before the onset of clinical symptoms or the rise of aminotransferases. In self-limiting infections, HBsAg becomes undetectable after 4 to 6 months. Its persistence beyond 6 months is the defining criterion to establish progression toward a chronic infection (5,6,7).

IgM Antibody against Hepatitis B Core Antigen (anti-HBc IgM): It is the cardinal and definitive marker to confirm the acuity of the infection. Its determination is indispensable, especially since in cases of rapid viral clearance, HBsAg might have been cleared from the serum at the time of initial medical presentation. Notably, low levels of anti-HBc IgM can also be detected during severe reactivation episodes of a chronic infection (8,9).

Hepatitis B e Antigen (HBeAg) and HBV DNA: HBeAg and viral DNA (HBV DNA) are identified in serum during the acute phase, reflecting active viral replication status and high patient infectivity. Quantifying HBV DNA also serves to monitor viral clearance kinetics (8,10).

Antibody to Hepatitis B Surface Antigen (anti-HBs): Its appearance occurs several weeks after the complete disappearance of HBsAg. The presence of anti-HBs confers long-term immunity against the virus and marks the protective resolution of the infection (8,10).

7. Therapeutic Implications of Early Identification

Most patients with acute hepatitis B experience spontaneous resolution and do not require specific antiviral treatment. However, clinical guidelines indicate that antiviral therapy should be considered in patients with severe forms characterized by significant hyperbilirubinemia, coagulation disorders, or acute liver failure (4).

Early identification of these patients directly depends on a timely clinical and serological diagnosis. In addition to enabling the early initiation of therapeutic measures, recognizing acute infection facilitates the implementation of secondary prevention strategies, including vaccination and close contact tracing.

Altogether, the available evidence demonstrates that the diagnostic approach to acute hepatitis B requires the integration of clinical, biochemical, and serological findings. Among all available markers, IgM anti-HBc remains the cornerstone for confirming recent acute infection, especially during the window period, while the combination of HBsAg, HBeAg, anti-HBe, anti-HBs, and HBV-DNA allows for an accurate characterization of disease progression and guides clinical decision-making.

8. Conclusion

In conclusion, the diagnostic approach to acute hepatitis B relies on the precise integration of clinical evaluation and serological profiling. While HBsAg identification marks active infection, IgM anti-HBc remains the definitive cornerstone for confirming recent acuity, particularly during the diagnostic challenge of the window period. Early and accurate interpretation of the complete viral panel—including HBeAg, anti-HBs, and HBV-DNA—is critical to guide clinical management, identify potential candidates for antiviral therapy in severe cases, and implement timely secondary prevention strategies to interrupt the chain of transmission.

Compliance with ethical standards

Disclosure of conflict of interest

The authors report no conflicts of interest for this article.

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