

## Acute hepatitis B or exacerbation of chronic hepatitis B-that is the question

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### Abstract

Hepatitis B virus (HBV) infection constitutes a serious global health problem. In countries with intermediate or high endemicity for HBV, exacerbations of chronic hepatitis B may be the first presentation of HBV infection. Some of these patients may be diagnosed mistakenly as having acute hepatitis B. Accurate diagnosis in these cases is very important for deciding whether to start treatment or not, because acute hepatitis B does not require therapy, while exacerbation of chronic hepatitis may benefit from it. Clinical and routine laboratory findings cannot help distinguishing between these two conditions. Therefore, several assays have been proposed for this purpose during the last few years. The presence of high levels of anti-HBe antibodies, HBsAg and HBV DNA are typical of chronic disease, whereas high titers of IgM anti-HBc, together with their high avidity index, characterize acute HBV infection. Starting from the description of a patient with acute hepatitis B-who recently came to our observation-we critically review the currently available assays that may help distinguishing between the different conditions and lead to the optimal management of each patient.

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### INTRODUCTION

Many parts of the world are endemic for the hepatitis B virus (HBV) infection. In these countries, especially those with intermediate or high endemicity rates, patients may frequently present with acute or chronic HBV infection. In fact, exacerbations of chronic hepatitis B are common, and may even be the first presentation of infection, including in cases with compensated, previously asymptomatic cirrhosis. Sometimes these patients may be diagnosed mistakenly as suffering from acute hepatitis B. At first glance, it is difficult to distinguish between these two clinical conditions, due to the similar clinical features and serological profile<sup>[1,2]</sup>. It is estimated that, in endemic areas, acute exacerbations of chronic hepatitis constitute about 50% of cases diagnosed as primary infections<sup>[2-5]</sup>. Distinguishing between these two conditions is extremely important, because antiviral therapy is not recommended in cases of acute hepatitis (except for very severe ones), whereas it is indicated in cases of chronic hepatitis. Therefore, simple, effective and reliable assays are required for differentiating between these conditions. Some methods for differentiating between chronic and acute infections have been suggested in the last few years, but no review summarized or compared them until now. Starting from the description of a case with acute hepatitis-who recently came to our observation-we shortly review these methods. Our aim is to provide practicing physicians with the basic knowledge and the tools useful for distinguishing between acute and chronic hepatitis B, for the benefit of the patients.

### CASE REPORT

A 38-year-old male presented to our emergency room

complaining of weakness, vomiting, sore throat and dark urines during the past few days. Several years before he had been diagnosed as having mixed connective tissue disease (MCTD), based on arthralgias and positive serology for ANA, anti-SSA/Ro and anti-SSB/La antibodies. He had been treated with plaquenil (hydroxychloroquine) for the previous 6 mo, but this drug had been discontinued two weeks before admission. The patient also had Wolff Parkinson White (WPW) syndrome for which he had never been treated. On admission, physical examination was unremarkable, except for the presence of a mild jaundice. Blood tests revealed extremely elevated liver enzymes, mostly hepatocellular, with ALT levels of 3069 U/L (normal: 6-53 U/L) and AST of 1215 U/L (normal: 2-60 U/L), while the indices of cholestasis were only mildly elevated, with alkaline phosphatase at 207 U/L (normal: 40-130 U/L) and GGT at 376 U/L (normal: 10-80 U/L). The total bilirubin was 35 mmol/L (normal: 0-17 mmol/L) and the LDH was 1200 U/L (normal: 300-620 U/L).

The patient denied traveling abroad, having unprotected sexual contact or recent viral infections. He had never received blood or blood-derived products, had never used drugs and he was not drinking alcohol. He had no fever and his electrocardiogram (ECG) was normal, with no signs of WPW syndrome.

#### **What is the differential diagnosis in this patient?**

The clinical presentation and the results of the laboratory tests call for a differential diagnosis of hepatitis. Since the patient had a diagnosis of MCTD the possibility of autoimmune hepatitis as an additional manifestation of his disease was raised<sup>[6]</sup>. In many of these cases, anti-smooth muscle antibodies (AMA) are positive, while in our patient they were negative. Another possible diagnosis would have been hepatic toxic injury due to plaquenil consumption, which is a reversible and dose-related cause of acute hepatitis<sup>[7]</sup>. Our patient had received plaquenil for 6 mo with no evidence of liver injury, and the treatment had been stopped 2 wk before admission. Furthermore, despite the discontinuation of the medication, liver tests were still worsening, making the diagnosis of plaquenil hepatotoxicity very unlikely. Thus, we had to look for infectious causes of hepatitis.

#### **What further investigations are needed?**

An abdominal ultrasound showed a liver of normal size and echogenicity, with an enlarged spleen (14.6 cm). The search for markers of autoimmunity revealed the presence of antinuclear (+2 of +4) and anti-SSA/Ro antibodies, but anti-SSB/La antibodies were negative and C3 levels were normal. Assays for ENA, anti-nRNP, anti-parietal, anti-mitochondria and anti-smooth muscle antibodies were negative. Blood tests for detecting infectious agents revealed the absence of serological markers of HAV, HCV and toxoplasmosis. However, there were markers suggesting a previous exposure to CMV and EBV (IgG antibodies). HBsAg and anti-HBc antibodies were positive. Further investigations revealed

the presence of HBeAg, the absence of anti-HBe antibodies, and  $2.65 \times 10^9$  IU/L of HBV DNA.

#### **What does this serologic profile implicate?**

Our patient had positive serology for HBV infection. The possibility of acute hepatitis B was raised, but the patient denied having unprotected sexual relations, using intravenous drugs, undergoing dental procedures or being exposed to blood products. Although in up to 30% of cases the exact mode of transmission cannot be identified, the lack of any risk factor for a recent infection does not support the diagnosis of acute infection. Therefore, we raised the possibility of an acute exacerbation of a chronic HBV infection. The differentiation between these two conditions is important because in cases of acute hepatitis, except for very severe ones, antiviral therapy is not recommended, whereas this is indicated in the case of an exacerbation of a chronic hepatitis. In both conditions, patients may suffer from flu-like prodromic symptoms, together with jaundice, abdominal discomfort and pruritus. Hepatosplenomegaly is also common in both situations. In addition, there are no significant differences as to the biochemical assays, such as peak bilirubin serum level, PT prolongation and serum albumin level. A tendency for higher levels of serum transaminases is seen in acute infection<sup>[8]</sup>. Some methods of differentiating between chronic and acute infections have been suggested over the past few years. A short review of some of them is described below, together with a discussion regarding their relevance to the present case.

**Role of HBeAg in the differential diagnosis:** HBeAg is a secretory protein that is processed from the precore protein and considered as a marker of HBV replication and infectivity<sup>[9]</sup>. The presence of HBeAg is usually associated with high levels of HBV DNA in serum and higher rates of transmission of infection from carrier mothers to their offspring and from patients to health care workers<sup>[10-13]</sup>.

Seroconversion from HBeAg carrier to anti-HBe antibodies occurs early in patients with acute infection, prior to HBsAg to anti-HBs seroconversion<sup>[14]</sup>. However, HBeAg seroconversion may be delayed for years in patients with chronic HBV infection. In such patients, the presence of HBeAg is usually associated with the detection of HBV DNA in serum and active liver disease (except for HBeAg-positive patients with perinatally acquired HBV infection, who may have normal serum ALT concentrations and minimal inflammation in the liver)<sup>[15,16]</sup>. Seroconversion from HBeAg to anti-HBe is usually associated with a decrease in serum HBV DNA levels and liver disease remission<sup>[17]</sup>.

HBeAg has been found more frequently in patients with acute infection compared with those with chronic infection, but the difference is not statistically significant. On the other hand, anti-HBe was found more frequently among patients suffering from an acute exacerbation of chronic infection than in those with acute infection. Levels of anti-HBe antibodies and HBeAg/anti-HBe

immune complexes are significantly higher in patients with exacerbation of chronic hepatitis<sup>[8,18]</sup>. However, the presence of anti-HBe as a diagnostic tool for chronic infection was found to have low sensitivity, specificity, NPV and PPV<sup>[8]</sup>.

Our patient had positive HBeAg and negative anti-HBe antibodies, which supports the diagnosis of an acute infection.

**Role of HBcAg in the differential diagnosis:** The viral core antigen is expressed within the infected hepatic cells and cannot be detected in serum. Its corresponding antibody, on the other hand, can be detected in serum at different phases of infection. IgM anti-HBc is a single serum marker of HBV infection within the period between the disappearance of HBsAg and the appearance of anti-HB antibodies. Identification of IgM anti-HBc is considered diagnostic for the acute phase of infection, but it has been reported that it can remain present in serum for two years from the initial infection. Moreover, the titer of IgM anti-HBc can also rise and become detectable in exacerbations of chronic hepatitis<sup>[18]</sup>.

Recently, it has been suggested that the titer of IgM anti-HBc can be useful for differentiating between acute and chronic HBV infection. Kumar *et al.*<sup>[8]</sup> demonstrated that high titers of IgM anti-HBc are more common in patients with acute infection, and titers above 1:1000 can be seen in up to 80% of these patients. In about 70% of patients with chronic hepatitis, IgM anti-HBc titers were lower than 1:1000 or negative. Differentiation between these two conditions by measuring the titers did not prove to have high sensitivity, specificity, NPV or PPV. Therefore another assay was proposed that enables the standardization between different laboratories, i.e. the sample/cutoff ratio (S/CO)<sup>[19]</sup>. A ratio > 10 indicates acute infection whereas a ratio < 10 indicates chronic infection. It appears that in cases of acute infection the mean ratio is 25.96, as opposed to an average ratio of 2.95 in chronic infection, a difference that is statistically highly significant. A S/CO > 10 had a sensitivity and NPV of 100%, a specificity of 99% and PPV of 99.3% for diagnosing an acute infection.

In our patient there were high titers (> 1:1000) of IgM anti-HBc, supporting the diagnosis of acute infection, but the S/CO (3.2/1.2) was < 10, suggesting a chronic infection.

**Role of HBsAg in the differential diagnosis:** HBsAg is an important marker of HBV infection. It has been reported that changes in quantitative measurement of this marker depend on the phase of infection<sup>[20-22]</sup>. A difference is found between the high levels of HBsAg that are detected in patients who are hospitalized during chronic or acute infection and the low levels observed in subjects with inactive, chronic infection. Moreover, recent data support the fact that high level of HBsAg are related to viral replication and disease activity<sup>[8]</sup>. In acute hepatitis, the levels of HBsAg are generally above  $1 \times 10^7$  IU/L and decrease sharply in the recovery phase.

In chronic anti-HBe-positive cases, HBsAg levels are generally lower than  $1 \times 10^7$  IU/L (mean 2655), whereas in 5 HBeAg positive chronic hepatitis patients the mean value was reported to be  $7.8756 \times 10^8$  IU/L, with 90% of cases exceeding  $1 \times 10^7$  IU/L.

Our patient had HBsAg levels of  $2.22 \times 10^9$  IU/L, which does not support an acute infection, but positive HBeAg and negative anti-HBe antibodies, which in chronic cases correlate with high levels of HBsAg.

**Role of HBV DNA in the differential diagnosis:** A quantitative measurement of the viral DNA enables the evaluation of the level of viral replication. There are many assays for measuring HBV DNA, their sensitivity being dependent on the assay used. Currently, there are some attempts to standardize the different measurements and express results in IU/L. Low or undetectable levels have been seen in patients suffering from acute hepatitis<sup>[21]</sup>, and a significant decline in HBV DNA levels has been reported even before the appearance of the disease. It has also been suggested that an acute infection may be diagnosed by finding undetectable HBV DNA in serum by the time medical aid is sought or in the presence of ALT levels lower than 400 IU/L. HBV DNA levels become detectable during reactivation of chronic hepatitis<sup>[22]</sup>. Recently, it has been shown that HBV DNA levels can help differentiate an acute infection progressing to recovery from an exacerbation of chronic infection, which requires therapy<sup>[8]</sup>. In this study, low levels of HBV DNA (< 0.5 pg/mL, equal to 141 500 copies/mL) were found in about 96% of patients with acute infection, as opposed to 13% in those with exacerbation of chronic hepatitis. Higher HBV DNA levels were found in 87% of patients with chronic infection compared to only 4% in those with acute infection. The sensitivity and specificity of low levels of HBV DNA for identifying an acute infection are 96% and 86.6%, respectively. The combination of high levels of HBV DNA with low titers of IgM anti-HBc yielded sensitivity, specificity, NPV and PPV of 100%, 97.9%, 96.3% and 100%, respectively, for diagnosing an exacerbation of a chronic hepatitis.

Our patient had high levels of HBV DNA (2650 000 copies/mL), which supports the diagnosis of exacerbation of chronic infection.

#### **What is the patient's diagnosis?**

Our patient had positive HBeAg, negative anti-HBe antibodies, and high titers of IgM anti-HBc, which support the diagnosis of an acute infection (Table 1). However, the presence of IgM anti-HBc S/CO < 10, low levels of HBsAg and high levels of HBV DNA suggest an acute exacerbation of chronic infection. In order to make a progress in the diagnosis, we decided to investigate his family. Familial analysis revealed positive anti-HBc in the patient's mother. She also recalled having icteric disease about 40 years earlier. Therefore, the possibility of perinatal transmission was raised and a diagnosis of acute exacerbation of a chronic HBV infection was made. The patient was treated with

Table 1 Comparison of the serological markers in acute HBV and in exacerbation of chronic HBV infections

Serological markers	Acute infection	Chronic exacerbation	Comments
HBeAg	-	+	Not different, and also not helpful in infections with HBeAg-negative strains
Anti-HBe	-	+	Low sensitivity and specificity, and also not helpful in infections with HBeAg-negative strains
Anti-HBe level, and complexes of HBeAg/anti-HBe	↓	↑	Not helpful in infections with HBeAg-negative strains
IgM anti-HBc	> 1:1000	< 1:1000	Low sensitivity, specificity, NPV and PPV
Sample/cutoff ratio for IgM anti-HBc	> 10	< 10	High sensitivity, specificity, NPV and PPV
Anti-HBc avidity index	< 0.7	> 0.7	High sensitivity, specificity, NPV and PPV
HBsAg	↓	↑	Useful in HBeAg-negative cases
HBV-DNA	< 0.5 pg/mL ≤ 141 500 copies/mL	> 0.5 pg/mL ≥ 141 500 copies/mL	Sensitivity: 96% Specificity: 86%

lamivudine, 100 mg per day, for 4 mo. After 2 mo of treatment the liver enzymes returned to normal values. After 4 mo of treatment, an HBeAg seroconversion was seen and anti-HBs antibodies appeared. The treatment was discontinued and after one year liver enzymes were still normal. The HBsAg/anti-HBs ratio indicated a complete recovery from the HBV infection.

## DISCUSSION

HBV infection remains a global public health problem, despite the availability of an effective vaccine. In most cases, HBV infection occurs in patients at high-risk, such as intravenous drug users, homosexual men and in certain groups where HBV is endemic. HBV infection can lead to an acute or chronic hepatitis, liver cirrhosis and hepatocellular carcinoma.

Acute HBV infection has a variable course, ranging from asymptomatic infection to fulminant hepatitis. The incubation period lasts from one to four months. A serum sickness-like syndrome may develop during the prodromal period, followed by systemic symptoms, anorexia, nausea, jaundice and right upper quadrant discomfort. The symptoms and jaundice generally disappear after one to three months. Some patients will develop chronic infection. The proportion of patients progressing to chronic infection is much higher in the newborn (up to 90%) compared to 1% to 5% among adults and intermediate values in young children. Most patients with chronic HBV infection are asymptomatic. However, in some patients, chronic HBV infection may be associated with extrahepatic manifestations such as panarteritis nodosa and glomerulonephritis. The natural history of chronic HBV infection is variable, depending upon age, mode of acquisition and ethnicity. Children in non-endemic countries frequently clear HBeAg and HBV DNA from serum during the first two decades of life. Children who seroconvert spontaneously tend to have higher ALT levels early in life<sup>[23]</sup>. By contrast, children from endemic countries in whom HBV was acquired perinatally usually remain HBeAg-positive and have high levels of viral replication, although histologic injury is typically mild<sup>[16,24]</sup>. These patients may experience acute exacerbations of hepatitis. Therefore, it may be difficult for their physicians to differentiate between those who have an acute hepatitis B from those with an exacerbation

of chronic HBV infection. The guidelines provided here may help solving this problem since the therapeutic approach toward these conditions is different. Antiviral therapy is recommended in case of acute exacerbation of chronic hepatitis B, whereas, in most cases, supportive treatment is sufficient in acute hepatitis B.

Key learning points: (1) In endemic areas, acute exacerbations of chronic HBV infection constitute about 50% of cases diagnosed as having acute HBV infection; (2) the proportion of patients progressing to chronic HBV infection is much higher in the newborn (up to 90%) compared with children or adults; (3) the therapeutic approach differs between acute hepatitis B and acute exacerbation of chronic hepatitis B, since treatment is usually not recommended in case of acute infection; (4) available laboratory tests can be helpful in the differential diagnosis, in order to provide a better management of patients.

## REFERENCES

- 1 **Chu CM**, Liaw YF, Pao CC, Huang MJ. The etiology of acute hepatitis superimposed upon previously unrecognized asymptomatic HBsAg carriers. *Hepatology* 1989; **9**: 452-456
- 2 **Tassopoulos NC**, Papaevangelou GJ, Sjogren MH, Roumeliotou-Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. *Gastroenterology* 1987; **92**: 1844-1850
- 3 **Chu CM**, Sheen IS, Liaw YF. The aetiology of acute hepatitis in Taiwan: acute hepatitis superimposed on HBsAg carrier state as the main aetiology of acute hepatitis in areas with high HBsAg carrier rate. *Infection* 1988; **16**: 233-237
- 4 **Liaw YF**, Chu CM, Huang MJ, Chen TJ, Lin DY. The etiology of acute viral hepatitis in an endemic area of hepatitis A and B. *Am J Trop Med Hyg* 1983; **32**: 1401-1406
- 5 Davis GL, Hoofnagle JH. Reactivation of chronic type B hepatitis presenting as acute viral hepatitis. *Ann Intern Med* 1985; **102**: 762-765
- 6 **Aoki S**, Tada Y, Ohta A, Koarada S, Ushiyama O, Suzuki N, Nagasawa K. [Autoimmune hepatitis associated with mixed connective tissue disease: report of a case and a review of the literature] *Nihon Rinsho Meneki Gakkai Kaishi* 2001; **24**: 75-80
- 7 **Giner Galvan V**, Oltra MR, Rueda D, Esteban MJ, Redon J. Severe acute hepatitis related to hydroxychloroquine in a woman with mixed connective tissue disease. *Clin Rheumatol* 2007; **26**: 971-972
- 8 **Kumar M**, Jain S, Sharma BC, Sarin SK. Differentiating acute hepatitis B from the first episode of symptomatic exacerbation of chronic hepatitis B. *Dig Dis Sci* 2006; **51**:

- 594-599
- 9 **Miller DJ**. Seroepidemiology of viral hepatitis: correlation with clinical findings. *Postgrad Med* 1980; **68**: 137-141, 144-148
  - 10 **Okada K**, Kamiyama I, Inomata M, Imai M, Miyakawa Y. e antigen and anti-e in the serum of asymptomatic carrier mothers as indicators of positive and negative transmission of hepatitis B virus to their infants. *N Engl J Med* 1976; **294**: 746-749
  - 11 **Beasley RP**, Trepo C, Stevens CE, Szmuness W. The e antigen and vertical transmission of hepatitis B surface antigen. *Am J Epidemiol* 1977; **105**: 94-98
  - 12 **Hwang LY**, Roggendorf M, Beasley RP, Deinhardt F. Perinatal transmission of hepatitis B virus: role of maternal HBeAg and anti-HBc IgM. *J Med Virol* 1985; **15**: 265-269
  - 13 **Alter HJ**, Seeff LB, Kaplan PM, McAuliffe VJ, Wright EC, Gerin JL, Purcell RH, Holland PV, Zimmerman HJ. Type B hepatitis: the infectivity of blood positive for e antigen and DNA polymerase after accidental needlestick exposure. *N Engl J Med* 1976; **295**: 909-913
  - 14 **Krugman S**, Overby LR, Mushahwar IK, Ling CM, Frosner GG, Deinhardt F. Viral hepatitis, type B. Studies on natural history and prevention re-examined. *N Engl J Med* 1979; **300**: 101-106
  - 15 **Chang MH**, Hwang LY, Hsu HC, Lee CY, Beasley RP. Prospective study of asymptomatic HBsAg carrier children infected in the perinatal period: clinical and liver histologic studies. *Hepatology* 1988; **8**: 374-377
  - 16 **Lok AS**, Lai CL. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. *Hepatology* 1988; **8**: 1130-1133
  - 17 **Hoofnagle JH**, Dusheiko GM, Seeff LB, Jones EA, Waggoner JG, Bales ZB. Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. *Ann Intern Med* 1981; **94**: 744-748
  - 18 **Maruyama T**, Schodel F, Iino S, Koike K, Yasuda K, Peterson D, Milich DR. Distinguishing between acute and symptomatic chronic hepatitis B virus infection. *Gastroenterology* 1994; **106**: 1006-1015
  - 19 **Rodella A**, Galli C, Terlenghi L, Perandin F, Bonfanti C, Manca N. Quantitative analysis of HBsAg, IgM anti-HBc and anti-HBc avidity in acute and chronic hepatitis B. *J Clin Virol* 2006; **37**: 206-212
  - 20 **Frosner GG**, Schomerus H, Wiedmann KH, Zachoval R, Bayerl B, Backer U, Gathof GA, Sugg U. Diagnostic significance of quantitative determination of hepatitis B surface antigen in acute and chronic hepatitis B infection. *Eur J Clin Microbiol* 1982; **1**: 52-58
  - 21 **Webster GJ**, Reignat S, Maini MK, Whalley SA, Ogg GS, King A, Brown D, Amlot PL, Williams R, Vergani D, Dusheiko GM, Bertolotti A. Incubation phase of acute hepatitis B in man: dynamic of cellular immune mechanisms. *Hepatology* 2000; **32**: 1117-1124
  - 22 **Gayno S**, Marcellin P, Lorient MA, Martinot-Peignoux M, Levy P, Erlinger S, Benhamou JP. Detection of serum HBV-DNA by polymerase chain reaction (PCR) in patients before reactivation of chronic hepatitis B. *J Hepatol* 1992; **14**: 357-360
  - 23 **Bortolotti F**, Cadrobbi P, Crivellaro C, Guido M, Rugge M, Noventa F, Calzia R, Realdi G. Long-term outcome of chronic type B hepatitis in patients who acquire hepatitis B virus infection in childhood. *Gastroenterology* 1990; **99**: 805-810
  - 24 **Lok AS**, Lai CL, Wu PC, Lau JY, Leung EK, Wong LS. Treatment of chronic hepatitis B with interferon: experience in Asian patients. *Semin Liver Dis* 1989; **9**: 249-253

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