CASE REPORT

# Acute hepatitis B virus infection and severe non-immune haemolytic anaemia: a rare relationship

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## SUMMARY

The clinical presentation of acute hepatitis B virus (HBV) infection is usually related to the onset of liver failure and damage. Anaemia may occur, but it is only rarely attributed to haemolysis. The authors report about the case of a 41-year-old woman with the diagnosis of acute HBV infection and coagulopathy (without encephalopathy) who developed non-immune haemolytic anaemia. Total recovery of the analytical liver profile, coagulopathy and anaemia was achieved through treatment targeting HBV.This case shows that, although rare, non-immune haemolytic anaemia may occur in association with acute HBV infection and that HBV suppression seems to lead to progressive anaemia resolution.

## BACKGROUND

The association between viral hepatitis and slight haemolysis is relatively frequent.[1] However, the relationship between acute viral hepatitis and non-immune haemolytic anaemia has been rarely described, is still poorly understood and usually occurs in patients with history of erythrocyte abnormalities and/or previous chronic liver disease.[2] In cases of acute hepatitis B virus (HBV) associated with immune haemolytic anaemia—although controversial—treatment with corticosteroids has proven to resolve the haematological dysfunction.[3 4] Notwithstanding, in the setting of non-immune haemolytic anaemia associated with acute HBV infection, corticosteroids do not have a precise role. HBV suppression, with antiviral agents, together with blood support transfusion might be the preferred approach.

## CASE PRESENTATION

A 41-year-old previously healthy woman presented to the emergency department with asthenia, nausea and choluria developing over 1 week. She was afebrile and haemodynamically stable on admission. On physical examination, the patient did not present signs of chronic liver disease. Yet, the patient was jaundiced and had pain on upper abdominal wall palpation, with no signs of peritoneal irritation or ascites. Hepatic encephalopathy was not observed. No family history of liver disease was registered. The patient was married and personal sexual history pretrained no relevance (one sexual partner, who tested negative for previous or chronic HBV infection).

## INVESTIGATIONS

On admission, blood analysis revealed aspartate aminotransferase (AST)=3178 U/L, alanine aminotransferase (ALT)=2889 U/L, gamma glutamyltransferase (GGT)=114 U/L, ALP=119 U/L, total bilirubin=22.9 mg/dL and direct bilirubin=19 mg/dL. Table 1 shows the chronic evolution of laboratory parameters. Renal function was normal. Coagulopathy with an INR of 1.7 was documented. Hepatitis A and C virus were negative, as was HIV-1 and −2. HBV serological profile showed positivity for HBsAg, IgM HBc, HBeAg and Anti-Hbe with negativity of Anti-HBs. The patient tested negative for: HDV, HEV, HSV-1 and −2, HZV, CMV. HBV viral load was $18\times10^5$ IU/mL. Abdominal ultrasound with Doppler showed no signs of portal or suprahepatic veins thrombosis and abdominal CT revealed a homogeneous liver and indirect signs of chronic liver disease were absent. The clinical scenario was interpreted as an acute HBV infection with acute liver injury (as documented by coagulopathy without hepatic encephalopathy). Furthermore, the patient presented with non-immune haemolytic anaemia (Hb=6 g/dL, normocytic and normochromic; reticulocytes=$185.68\times10^9$/L) characterised by low haptoglobin levels (<0.24 g/L; normal range 0.25–1.90 g/L), high lactate dehydrogenase (1163 U/L) and negative direct and indirect Coombs test—cold agglutinin titre was normal. The patient did not have a mechanic heart valve, glucose-6-phosphate dehydrogenase deficit was excluded and there was no evidence of acanthocytosis. The peripheral blood smear was normal and other red blood cell (RBC) defects were excluded (such as haemoglobin disorders, RBC enzyme dysfunction, thrombotic microangiopathies, drugs or metal toxicities, thalassemias and paroxysmal nocturnal haemolytic anaemia).

The patient was admitted in the intermediate care unit for treatment, follow-up and further investigation.

## TREATMENT

Treatment with entecavir (1 mg/day) and a 5-day N-acetylcystein protocol was initiated.

The patient was also started on folic acid and vitamin K (administered for 3 days).

## OUTCOME AND FOLLOW-UP

During the hospital stay, bilirubin levels and INR normalised progressively. Encephalopathy was not documented throughout. Haemoglobin levels

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**Table 1** Evolution of laboratory parameters

| | Day 1 | Day 2 | Day 3 | Day 6 | Day 7 | Day 9 | At 4 months |
|---|---|---|---|---|---|---|---|
| TB in mg/dL | 22.9 | 24.1 | 21.9 | 15.2 | 12.08 | 7.7 | 0.68 |
| DB in mg/dL | 19 | 18.8 | 20.3 | 13.5 | 10.3 | 6.9 | 0.18 |
| IB in mg/dL | 2.9 | 4.5 | 1.5 | 1.6 | 1.7 | 0.8 | - |
| AST in U/L at 37° | 3178 | 3272 | 3101 | 1089 | 785 | 465 | 23 |
| ALT in U/L at 37° | 2889 | 2869 | 2585 | 1499 | 1195 | 716 | 13 |
| AF in U/L at 37° | 119 | 131 | 142 | 204 | 202 | 166 | 63 |
| GGT in U/L at 37° | 114 | 142 | 148 | 263 | 261 | 226 | 14 |
| LDH in U/L at 37° | 1163 | 1261 | 463 | 369 | 300 | 297 | 190 |
| Hb in g/dL | 6.2 | 7.1 | 7.6 | 8.3 | 8.1 | 8.7 | 12.6 |
| HBV viral load in UI/mL | $18\times10^5$ | | | | | | <20 |

AF, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, direct bilirubin; GGT, gamma glutamyltransferase; Hb, haemoglobin; HBV, hepatitis B virus; IB, indirect bilirubin; LHD, lactate dehydrogenase; TB, total bilirubin.

increased and stabilised. Blood transfusions were not required. The patient was discharged home with total bilirubin of 6.7 mg/dL, INR of 1.1 and Hb of 11 g/dL; she maintained treatment with entecavir. At 4 months of follow-up, the patient had the following analytic profile (see table 1):

AST=23 U/L, ALT=13 U/L, GGT=14 U/L, ALP=63 U/L, Hb=12,6 g/dL, INR=1, total bilirubin=0.68 mg/dL, direct bilirubin=0.18 mg/dL, HBV viral load <20 IU/mL, negative HBsAg and positive anti-HBs (156.1 UI/L) and anti-HBc.

## DISCUSSION

The association of acute hepatitis—specifically hepatitis B—and non-immune haemolytic anaemia is rare.[5] It occurs usually in young patients without a significant medical history and presents with haemoglobin levels usually below 8 g/dL, as depicted in the case described above. Only a few cases of this severe association have been described so far, and there is usually an associated erythrocyte disorder. The development of anaemia generally occurs in the recovery phase of hepatitis, which was not reflected in this case—it was coincidental with liver dysfunction.[5] In the majority of described cases (6/8), treatment with corticosteroids and/or blood transfusion was required. However, in this case, supportive treatment did not play an essential role, as after initiation of treatment targeting HBV suppression, a progressive and sustained resolution of dysfunctions was observed. In all patients described in literature, the association of acute HBV and non-immune haemolytic anaemia led to a prolonged hospital stay and increased rate of complications (organ dysfunction in 7/8 patients and death in 2).[6] The pathophysiology of this association remains unknown, which may be virus related, linked to host susceptibility factors or due to liver failure itself. An accurate and prompt diagnostic work-up of anaemia is of uttermost importance to exclude other confounding aetiologies (such as RBC abnormalities), which may imply a different treatment approach. From our point of view, treating the cause (HBV infection) should equally be the mainstay treatment of associated non-immune haemolytic anaemia. In this particular case, entecavir was initiated due to high total bilirubin values (>10 mg/dL) and evidence of coagulation dysfunction (INR >1.6).[7] The association of N-acetylcystein (5-day protocol) followed current recommendations for treatment of acute liver failure irrespective of aetiology.

## Learning points

- Non-immune haemolytic anaemia related to acute hepatitis B virus (HBV) infection is a rare entity.
- Its recognition is of major importance as it is related to increased hospital stay and vulnerability to complications.
- Non-immune haemolytic anaemia treatment, in this setting, is based on HBV suppression.

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## REFERENCES

1 Chau TN, Lai ST, Lai JY, *et al*. Haemolysis complicating acute viral hepatitis in patients with normal or deficient glucose-6-phosphate dehydrogenase activity. *Scand J Infect Dis* 1997;29:551–3.
2 Raffensperger EC. Acute acquired hemolytic anemia in association with acute viral hepatitis. *Ann Intern Med* 1958;48:1243–53.
3 Lapp RT, Rochling F. Acute cholestatic hepatitis a virus infection presenting with hemolytic anemia and renal failure: a case report. *Case Reports Hepatol* 2013;2013:1–4.
4 European Association for the Study of the Liver. EASL clinical practice guidelines: management of cholestatic liver diseases. *J Hepatol* 2009;51:237–67.
5 Vanderhoof JA, Ament ME. Severe Coombs negative hemolytic anemia in hepatitis B. *West J Med* 1976;125:228–30.
6 Wang M, Yap F, Joynt G. Case Report: Severe non-immune mediated haemolytic anaemia associated with acute hepatitis B and E co-infection in a patient with normal G6PD levels. *F1000Res* 2015;4:1002.
7 Jindal A, Kumar M, Sarin SK. Management of acute hepatitis B and reactivation of hepatitis B. *Liver Int* 2013;33(Suppl 1):164–75.