A Rare Case of Acute Hepatitis B Virus Infection Causing Guillain-Barré Syndrome

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Viral hepatitis has rarely been implicated in the acute immune-mediated polyneuropathies that are classified under the term Guillain-Barré syndrome (GBS); these associations have accounted for approximately 1% of GBS cases.[1] In this case study, we present a patient with GBS and acute hepatitis B virus (HBV) infection, and we emphasize the importance of being aware of the association between these 2 diseases, as early diagnosis and timely initiation of treatment determine neurologic recovery from GBS.

Case Report

A 42-year-old Vietnamese woman presented with a 2-week history of nausea, vomiting, and abdominal pain and a 1-week history of jaundice. She recalled development of a trauma-induced laceration to the right side of her face. An open wound had been present approximately 4–6 weeks before her presentation. No other risk factor for an acute hepatitis virus infection was identified. A review of the patient's systems revealed a headache and generalized fatigue; the patient did not have other neurologic complaints.

A physical examination revealed stable vital signs, and there was no evidence of hepatic encephalopathy. Her right cheek was completely healed without evidence of infection. She had icteric sclera and right upper quadrant abdominal tenderness to palpation. Her skin was jaundiced, and she had no neurologic deficits.

Diagnostic evaluations showed a normal complete blood count and basic metabolic panel. The patient had a total serum bilirubin level of 14.4 mg/dL, a direct bilirubin level of 10.8 mg/dL, an aspartate aminotransferase level of 850 IU/L, an alanine aminotransferase level of 1,817 IU/L, an alkaline phosphatase level of 211 IU/L, a total protein level of 7.4 g/dL, a serum albumin level of 3.7 g/dL, and an international normalized ratio of 1.2. The patient was positive for hepatitis B surface antigen (HBsAg), immunoglobulin (Ig) M antibody to hepatitis B core antibody, and HBV DNA real-time polymerase chain reaction (PCR; 1,850 IU/mL). Serologic and PCR tests for hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus were negative. We were able to document prior seronegativity for HBsAg and hepatitis B core IgG antibody 5 years prior to this presentation. Serologic tests for hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, Epstein-Barr virus, cytomegalovirus, and HIV were negative. An ultrasound of the abdomen showed increased echogenicity of the liver with normal size and Doppler flow as well as waveforms in all hepatic vasculature without mass, ascites, gallstones, or biliary obstruction. A computed tomography scan of the abdomen and pelvis revealed a normal-sized liver and spleen with mild periportal edema.

Due to the severity of the patient's illness, antiviral treatment with a nucleoside polymerase inhibitor was started. Over the ensuing days, her transaminase and bilirubin levels began to improve. On Hospital Day 4, numbness of the fingers developed as well as difficulty speaking and swallowing. The patient's neurologic symptoms progressed rapidly. She had difficulty clearing her oral secretions and experienced rapidly worsening ascending weakness in her bilateral upper and lower extremities on Hospital Day 5. On physical examination, no deep tendon reflexes were present in her bilateral extremities, and her sensation to gross touch

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was slightly decreased. She was subsequently transferred to the intensive care unit and was intubated for airway protection. A diagnosis of GBS was strongly suspected. A lumbar puncture with cerebrospinal fluid (CSF) analysis showed a white blood cell (WBC) count of 1/mm^3, a red blood cell count of 9/mm^3, a total protein level of 71 mg/dL, and a glucose level of 123 mg/dL, which are consistent with the classic finding of albuminocytologic dissociation (an elevated CSF protein level with a normal CSF WBC). This finding is present in 80–90% of patients with GBS 1 week after the onset of symptoms.[2] Electromyography and a nerve conduction study showed severe sensorimotor polyneuropathy with axonal features overlying moderate-to-severe demyelination. Coupled with the patient's clinical presentation, these findings confirmed the diagnosis of GBS, which was thought to be secondary to acute HBV infection.

Treatment with intravenous immunoglobulin (IVIG) was started on Hospital Day 6 and continued for 5 days. The patient's weakness slowly started to improve over the next few days. She was extubated after 1 week of mechanical ventilation and was transferred to an acute rehabilitation center, where she continued to slowly improve.

After a 6-week stay at the center, the patient was discharged home with complete independence for her daily living activities and very minimal assistance for walking on flat surfaces and stairs. Her dysphagia had resolved, and she had achieved full bowel and bladder control. Three months after discharge from the center, she was seen at our hepatology clinic, where she demonstrated ambulation without assistance. Her laboratory test results showed undetectable HBV DNA levels, negative HBsAg, and positive hepatitis B surface antibody and hepatitis B e antibody, indicating successful seroclearance of her acute HBV infection.

Discussion

GBS has been rarely reported in association with acute viral hepatitis. The first reported case of GBS in the setting of acute HBV infection dates back to 1953.[3] Fewer than 20 cases of GBS complicating acute HBV infection have been reported to date. The last reported case, which was published in 2003, consisted of a patient with GBS who was in a preicteric stage of acute HBV infection.[4]

Successful treatment of GBS requires early diagnosis and timely administration of IVIG or plasma exchange (PE). At 4 weeks after receiving PE daily for 3–5 days, patients showed greater improvements in disability grades compared with patients receiving supportive care alone. At 1 year post-treatment, the need for mechanical ventilation was less and the median time in days to recover independent walking as well as status concerning death or disability were significantly better in patients who received PE than in those who received supportive care alone.[5] IVIG also has been shown to be as effective as PE, and no difference was seen in recovery measures when comparing PE followed by IVIG with either treatment alone.[6] It is particularly important to diagnose GBS promptly and initiate therapy early, as PE has been shown to be most effective when started within 7 days of symptom onset.[4]

Several mechanisms have been proposed to explain how HBV causes GBS. One proposed mechanism involves molecular mimicry between HBV DNA and myelin basic protein, whereby initial host immunity to HBV leads to the subsequent antibody-mediated attack of the myelin sheath. Other proposed mechanisms have included HBsAg-mediated immune complex (IC) vasculitis and direct damage to the myelin sheath by HBV.[4] HBsAg has been found in the CSF of some patients with GBS.[4,7-9] Titers of serum and CSF ICs containing HBsAg have been reported to decrease concomitantly with improvement of neurologic symptoms, implicating their potential involvement in the pathogenesis of GBS.[8-9] Tsukada and associates demonstrated the presence of immunofluorescent deposits of ICs containing HBV in the vasa nervorum of a patient with chronic relapsing polyneuropathy that was associated with chronic HBV infection.[9] The same group of researchers later reported that the cycles of remission and exacerbation of neurologic symptoms paralleled liver dysfunction.[10]

It has been debated whether HBsAg in the CSF crosses the blood brain barrier (BBB) from systemic circulation or if it is locally generated within the CSF. HBsAg has been identified in the CSF of patients with plasma that is positive for HBsAg but without active liver disease.[11] In these patients, possible mechanisms that explain the presence of HBsAg in the CSF include a change in the permeability of the BBB, leakage into the CSF due to lumbar punctures, or pathologic involvement of the meninges (such as in leukemia).[7] Penner and colleagues reported a patient with acute HBV infection complicated by GBS who had high levels of circulating HBsAg containing ICs in the serum and CSF during the acute GBS phase; the patient experienced clearance of the ICs with neurologic recovery.[8] This would indicate that the CSF ICs are likely derived from systemic circulation.[8] On the other hand, Feutren and coworkers reported a patient with GBS and acute HBV infection who demonstrated intrathecal synthesis of viral antigen-containing ICs, suggesting the extension of viral infection to the central nervous system.[7] However, a report by Huet and associates argued that HBsAg usually does not cross the BBB, and in GBS, the viral antigen may instead enter through the demyelinated nerve roots.[12,13] Although the exact pathophysiology of GBS related to acute HBV infection remains unclear, the

association of these 2 conditions is well documented, as seen in this case report as well as earlier case reports.

Conclusion

Acute HBV infection is rarely associated with GBS. Because early diagnosis and timely administration of IVIG or PE improve the degree of neurologic recovery, gastroenterologists should be aware of this association.

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Review

Extrahepatic Manifestations of Acute Hepatitis B Virus Infection

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Hepatitis B virus (HBV) infection leads to a number of hepatic complications, including acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Although uncommon, several immune-mediated extrahepatic manifestations may develop during both acute and chronic HBV infection.

Presentation of Hepatitis B Virus Infection

HBV infection leads to a wide spectrum of liver disease, including acute hepatitis, fulminant liver failure, chronic hepatitis, cirrhosis, and hepatocellular carcinoma.[1] Acute HBV infection is often a mild, asymptomatic, subclinical illness that frequently passes without detection in approximately two thirds of cases.[2] Symptoms of acute HBV infection are often nonspecific, and diagnosis is secured through serologic testing for immunoglobulin (Ig) M antibody to hepatitis B core antigen. Clinical evidence of hepatitis—fatigue, nausea, or worse (jaundice and, occasionally, acute liver failure)—develops in approximately one third of patients with acute HBV infection. The time frame for clinical incubation of acute HBV infection averages 2–3 months; however, this time frame can range from 1–6 months after exposure. There is some evidence that the time of incubation correlates with the size of the viral load.[3] Rarely, acute and chronic HBV infection can be associated with extrahepatic conditions.

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Extrahepatic Manifestations

Although HBV primarily affects hepatocytes, it has also been shown to cause complications in other organs. Several of these manifestations have been described, and several of them are now well established.[4] These extrahepatic manifestations are nonspecific for HBV infection. Table 1 provides an overview of the distinct conditions for which HBV is the specific etiology. The pathophysiology of these associated symptoms is mainly based on immune complex reactions that occur in the skin, joints, muscles, and kidneys. Awareness and recognition of these manifestations are of the highest importance for facilitating early diagnosis and treatment.[5]