Cryptogenic chronic liver disease in India: what is the role of hepatitis B?

The report by Radhakrishnan et al. in this issue of the Journal presents data on silent/occult hepatitis B infection in patients with chronic liver disease. A total of 71 patients with chronic liver disease were studied: 9 of them were HBsAg-positive. All 9 (4 HBeAg-positive as well) had detectable HBV DNA by polymerase chain reaction (PCR) in serum. Of the 62 HBsAg-negative patients, 2 (3.2%) had detectable HBV DNA. These two patients had evidence of past exposure to hepatitis B and were anti-HBe antibody-positive (as were 36 others). Both had evidence of cirrhosis on histology. Twenty-six of the 62 had evidence of hepatitis C infection.

This is the first study from India on the role of occult hepatitis B in the causation of chronic liver disease. The sample size in this study is too small to derive firm conclusions. Clinical data on other factors that may contribute to the development of chronic liver disease, e.g., alcohol abuse, diabetes, obesity, are not available. Histological data are available in only a small subset, which makes it difficult to assess the role of HBV DNA in the final outcome. In the two HBsAg-negative patients with detectable HBV DNA, DNA sequence analysis has not been done to determine type of mutation if any. Despite these concerns this is an important step towards defining the role of hepatitis viruses in cryptogenic liver disease in the Indian subcontinent.

In the majority of patients with chronic liver disease, the clinical data, pattern of abnormal liver profile, and serological markers, along with histology, will identify the etiology of liver disease. However, in 10%-30% of cases, the cause remains obscure; we label them as idiopathic or cryptogenic. With the advent of PCR allowing detection of HBV DNA and HCV RNA in patients who lack antibodies, the problem of occult hepatitis infection and coinfection is increasingly recognized. Data on this aspect have been highly variable, depending on the region from which it is published and the prevalence of hepatitis B infection in that population.

One of the earliest studies, done in France by Brechot et al., before the discovery of hepatitis C and PCR, showed the presence of HBV DNA (by hybridization) in 10% of serum samples and 59% of liver tissue specimens from patients with chronic liver disease who were HBsAg-negative. Cacciola et al. from Sicily (Italy) reported HBV DNA in the sera of one-third of 200 patients with hepatitis C-related liver disease (all were HBsAg-negative). One-third of those positive for HBV DNA had no serum markers suggestive of past exposure to hepatitis B. Berasain et al. from Spain recently published a study looking at virological findings in their group of patients with cryptogenic chronic liver disease. Of the cohort of 1075 patients, 10% were labeled cryptogenic after initial detailed work-up. Of these, 18% were HBV DNA-positive (50% of these had no serum markers of past HBV infection), and 8% were HCV RNA-positive.

Studies from Japan and China, which are hyper-endemic zones for hepatitis B, have shown 70%-90% of patients with 'idiopathic' liver disease to have HBV DNA by PCR in their sera. Also, studies from various parts of the world in HBsAg-negative patients with hepatocellular carcinoma suggest a significant contribution of occult hepatitis B to its causation.

The only other study from India, from Lucknow, looked at serological and virological data in 56 patients with chronic liver disease. Of the 35 patients initially labeled as cryptogenic, 57% tested positive for hepatitis B by PCR; in addition, one-third of patients thought to have alcohol-related liver disease also were HBV DNA-positive. Liver tissues tested for HBV DNA, in patients with negative serum HBV DNA, found an additional 4 cases to be positive. The authors concluded that hepatitis B was the most common cause associated with 'cryptogenic' liver disease in their patients. Another study in patients with acute hepatic failure found that 40% of 'cryptogenic' cases were HBV DNA-positive and 9% were HCV RNA-positive.

There are several reasons postulated for HBV DNA positivity in HBsAg-negative sera. HBsAg could be present at a level too low for detection by conventional assays. Antigen could be hidden in the HBs antigen-immune complex. Deletion, mutation, or rearrangement of HBV surface gene or viral integration could lead to HbsAg negativity. Hepatitis B variants with different antigenicity and immunogenicity may exist.

Studies on HBV DNA sequencing from Japan and USA in HBsAg-negative but HBV DNA-positive patients with chronic liver disease or hepatocellular carcinoma have shown mutation in the X gene-coding region, leading to suppression of replication and expression of HBV DNA, resulting in HBsAg negativity. The only study available from India, from Delhi, looking at DNA analysis in their cohort of HBV DNA-positive, HBsAg-negative patients with chronic liver disease reported surface gene mutations previously described in vaccine escape mutants. We need more studies on cloning and sequencing of HBV DNA from India to know the type of mutations our patients harbor.

We have very few studies looking at the clinical implication of HBsAg-negative chronic liver disease. The
study by Berasain et al. showed that patients with cirrhosis were more likely to have occult HBV infection as a cause of chronic liver disease. Cacciola et al. showed that their patients with hepatitis C with occult HBV infection were more likely to have cirrhosis on initial histology than those without; these patients also had significantly lower response to interferon treatment.

Huo et al. followed up 1355 chronic carriers of the hepatitis B virus for 12 years. HBsAg cleared in 4% of subjects. Of these, 31% had detectable HBV DNA in serum. Despite clearing of HBsAg, 33% developed a liver complication. The authors concluded that these patients had hepatitis B infection for many years before clearing HBsAg. This had led to chronic liver injury and viral genome integration, predisposing to development of cirrhosis and hepatocellular carcinoma. These occurred irrespective of the presence or absence of detectable HBV DNA at this stage.

However, Chung et al. had contrary results. They followed up 121 patients with hepatitis B-related cirrhosis; 5% cleared HBsAg after mean 9.1 (6.2) years. Of these, 67% had detectable HBV DNA; however, 83% had improvement in liver function. All of them remained alive on follow up, whereas a third of those who did not clear HBsAg died and another third had deterioration in liver function.

As virological techniques improve, we will continue to redefine cryptogenic liver disease. We need to generate more data from our country before we can arrive at a consensus on how far to investigate these patients and develop an algorithm for the management of cryptogenic liver disease in India.

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References

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