Hepatitis B virus genotyping: will it stand the test of time?

Hepatitis B virus (HBV) has been classified into 8 genotypes (A-H) based on intergroup divergence of 8% or more in the complete nucleotide sequence. The distribution of HBV genotypes may vary with time and with population migration, as has been demonstrated in the United States. Further, we know that there are many subtypes within some genotypes.

There has been an explosion of knowledge with respect to HBV genotypes and their association with HBV core antigen, HBeAg seroconversion, activity of liver disease, and treatment response. Data on the clinical relevance of HBV genotypes are not available from many parts of the world. Most of the information today is based on studies of patients with chronic HBV infection in Asia. Since B and C are the predominant genotypes reported from Asian countries, these studies are restricted to comparison of patients with these two genotypes. These studies help us to understand the relationship of HBV genotypes B and C with the rate of progression of liver disease, since the age of onset of infection is presumed to be the same (perinatal period) in the vast majority of patients.

Studies suggest that genotype B is associated with spontaneous HBeAg seroconversion at a younger age, less active liver disease, and a slower progression to cirrhosis compared to genotype C. Further, the patients are less likely to have hepatitis flares and more likely to remain in remission after HBeAg seroconversion. It is interesting to know that hepatocellular carcinoma (HCC) in Japan occurs less frequently with genotype B and occurs at an older age. It is believed that shorter duration of high level of HBV replication and less active necro-inflammation may contribute to a more favorable outcome among patients with genotype B.

There is only one study from Taiwan that contradicts this belief; in this study, genotype B (all subtypes) was more frequently encountered in patients with HCC aged less than 50 years, suggesting that it may be associated with accelerated progression to HCC.

Genotypes A and D have been reported from Western Europe and North America; in the Mediterranean region, the Middle East, and Central Asia genotype D is dominant. Limited data from India suggest that genotypes A and D are most prevalent but their relationship to severity of disease is not known.

Kumar et al report in this issue of the Journal that genotype A is more often associated with ALT elevation, core antigen positivity, absence of anti-HBe in patients aged 25 years and above, and more frequently with cirrhosis of liver as compared to genotype D. Further, one of their cases had genotype C, which has not been previously reported from India. Studies from India have generally reported predominance of genotype D. This raises the possibility that the Indian population originally had genotype D, which has been replaced by genotype A particularly in northern India due to human migration from Europe over time.

There is lack of information about the clinical course of patients with genotypes other than B and C. A study from Spain reported that core antigen seroconversion rates were similar with genotypes A and D, but sustained biochemical and virological remission was not common with patients with genotype A who had HBeAg seroconversion. These patients had also higher rates of HBsAg clearance. The study also showed that patients with genotype F were more likely to die from liver disease than those with A and D.

We do not have data comparing HBeAg seroconversion, activity of liver disease, and rate of progression to cirrhosis and liver cancer among patients with all known HBV genotypes. In a cross-sectional study of 694 patients in USA, genotypes B and D were associated with lower prevalence of HBeAg than genotype A, while genotype B was associated with lower rate of hepatic decompensation compared to genotypes A, C and D. HBV genotype has been reported to correlate with response to interferon. Two studies from Asia found that genotype B had a higher rate of HBeAg seroconversion compared to genotype C. Another study, from Spain, suggested that genotype A had a higher rate of seroconversion than genotype D.

Recent studies with pegylated interferon (IFN) confirmed that HBeAg seroconversion occurred more often with genotypes A (47%) and B (44%) as compared to genotypes C (28%) and D (25%). It will be interesting to find out whether HBV genotype plays a role in response to IFN amongst patients with e antigen-negative chronic hepatitis. Unlike IFN, there is little data on the correlation between HBV genotype A and response to lamivudine or adefovir dipivoxil therapy. A recent study based on 78 German patients reported that lamivudine-resistant mutants emerged more rapidly with genotype A versus D, but the correlation with response was not reported. Thakur et al report in this issue of the Journal that genotype D is more likely to have sustained viral response after lamivudine therapy as compared to genotype A. Retrospective analysis of three clinical trials of adefovir dipivoxil showed that all HBV genotypes had similar decrease in serum HBV DNA levels, but a correlation with HBeAg seroconversion could...
not be ascertained because of small number of patients with HBeAg seroconversion. There is also paucity of information on the correlation between HBV genotypes and outcome of acute HBV infection. A report from Switzerland showed that 80 patients with acute HBV had genotype D and 80 patients with chronic hepatitis B had genotype A. This leads us to believe that different genotypes may be associated with different rates of progression from acute to chronic HBV infection.

Studies based on full length of HBV sequence in patients with fulminant hepatitis showed that 3 sequences in fulminant cases were identical and represented the major sequence of the outbreak strain. The remaining 4 fulminant cases differed by 1-9 nucleotide sequences, while the sequence from the two control subjects differed by 2-9 nucleotides. These data indicate that, based on genomic sequences, we can confirm a common-source outbreak and the HBV strain identified did not invariably lead to fulminant course. Further, more analysis of full-length HBV genome sequences in other cases of fulminant hepatitis B failed to identify consistent mutations.

In summary, HBV genotypes correlate with the clinical outcome of chronic HBV infection and response to treatment. The evidence is stronger between genotypes B and C and response to interferon but not to nucleoside or nucleotide treatment. There is also a clear association between HBV genotypes and precore and core promoter mutation. Genotyping of HBV may remain a research tool unless we prove that it can predict the risk of adverse outcomes (fulminant disease, cirrhosis, HCC) or can influence decision-making in management.

Premashish Kar
Department of Medicine and Gastroenterology Division, Maulana Azad Medical College, New Delhi 110 002

References

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Correspondence to: Dr Kar, D-II/M-2755, Netaji Nagar, New Delhi, 110 023. Fax: (11) 2323 0132. E-mail: pkar@vsnl.com