

HBV JOURNAL REVIEW

Volume 4, Issue 11

November 01, 2007

Hepatitis B

Christine Kukka

Experts Call for Revised Hepatitis B Diagnostic Tests

As more is learned about hepatitis B virus (HBV) infection, researchers are finding that the current lab tests used to diagnose and monitor chronic hepatitis B infections are inadequate.

Writing in the October 2007 issue of the *Journal of Viral Hepatitis*, a team of German researchers say the diagnostic test regimens do not identify “occult” HBV infections. These occult or hidden infections are defined by undetectable hepatitis B surface antigen (HBsAg), but detectable HBV DNA (viral load or viruses in the blood) and hepatitis B core antibody (anti-HBc).

This is a huge deviation from textbook and medical guidelines that define an HBV infection if HBsAg is present.

“Deviations from these patterns occur in the very early phase, in low-level (or occult) infection and under immunosuppression,” researchers wrote. “In order to obtain a reliable diagnosis under these conditions, tests for all three markers of HBV infection have to be applied: HBsAg, HBV DNA and anti-HBc. All tests should be as sensitive as feasible, but even then occult infection may be missed. Reliable detection of occult or mutated HBV is particularly important in blood and organ donors and in patients before or with immunosuppression.”

Another article in the journal also suggests that viral mutations and genotypes, often resulting from antiviral therapy, may also alter the HBsAg molecular make-up, which can also mask it from current diagnostic lab tests, which is why the additional HBV DNA test is critical.

Iron Overload Linked to Liver Cancer in Hepatitis B Patients

It has been suggested that diets rich in iron may hasten liver damage or contribute to liver cancer when there is viral hepatitis infection present. A team of U.S. researchers, writing in the October 2007 issue of *Liver International*, examined the link between iron overload in the liver and

HBV Journal Review

A publication of the Hepatitis C Support Project

Executive Director

Editor-in-Chief,
HCSP Publications
Alan Franciscus

Contributor

Christine Kukka

Managing Editor,

Webmaster
C.D. Mazoff, PhD

Contact Information:

The Hepatitis C Support Project

PO Box 427037
San Francisco, CA 94142

www.hbvadvocate.org

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liver cancer in 5,224 patients who underwent liver transplantation for end-stage liver disease caused by a variety of infections and diseases.

Both iron overload and liver cancer was most common in patients with hepatitis B (16.7% of patients), followed by patients with hepatitis C (15.1%).

Researchers concluded that any iron overload was significantly associated with liver cancer, no matter what disease or illness led to the liver damage.

Reactivation after HBeAg Seroconversion More Likely in Men, Patients with Genotype C, and Those with Prior High Viral Loads

Once a patient loses the hepatitis B “e” antigen (HBeAg), and develops the “e” antibody (called seroconversion), many assume they will have lower viral load (HBV DNA) and less liver damage. Not so, according to a report by Taiwanese researchers published in a recent issue of *Gastroenterology*.

Researchers followed 75 men and 58 women who initially tested positive for HBeAg and then experienced HBeAg seroconversion to see if their viral load would rebound, and if they experienced liver damage, shown by increased levels of alanine aminotransferase (ALT) after seroconversion. ALT is an enzyme released by damaged or dying liver cells.

The patients were followed for nearly seven years, and on average were age 28 at the start of the study. Most had genotype or HBV strain B, and 25 had genotype C.

Reactivation of hepatitis B (resurgence of HBV DNA and elevated ALT levels) occurred in 26 patients and more commonly in those with genotype C, who were male, who had high HBV DNA levels before their HBeAg seroconversion, and who were older than age 40.

Researchers suggest that in addition to gender and genotype, HBV reactivation may be more likely if there were more HBV DNA to combat to begin with, and if it took many years for the immune system to finally eliminate the HBeAg.

Telbivudine More Powerful Than Adefovir at Lowering HBV DNA

The antiviral telbivudine (Tyzeka) appears to be a more effective than the antiviral adefovir (Hepsera), according to the results of an open-label, randomized controlled trial published Oct. 1, 2007, in the *Annals of Internal Medicine*.

At 16 clinics, 131 HBeAg-positive patients, who had never been treated, were randomly assigned to receive telbivudine, adefovir, or 24 weeks of adefovir followed by 28 weeks of telbivudine treatment.

The goal was to see which treatment achieved the greatest decline of HBV DNA at week 24, and at week 52.

The average decrease in HBV DNA at week 24 was greater in the telbivudine group than in either other group (a drop of 6-fold vs. 4.9-fold). In addition, more patients in the telbivudine group had undetectable viral load at week 24 (39% vs 12%).

After 52 weeks, HBV DNA suppression was

greater in patients who had received continuous telbivudine or were switched to telbivudine after 24 weeks than in those who received continuous adefovir.

“Data from this study support the concept that maximizing viral suppression early in the course of therapy is linked to improved efficacy responses and less resistance, suggesting that agents providing the greatest viral suppression may be preferable as initial therapy,” the authors concluded.

T Cells That Fight Chronic Viral Infections Become Progressively Exhausted

A new study of the immune cells that battle chronic viral infections shows that these T cells become exhausted by the fight and undergo profound changes that make them progressively less effective to fight infection over time.

The findings also suggest that new therapies could be developed to reinvigorate T cells that become depleted in their struggle against a virus.

Alternatively, strategies that intentionally trigger the immune-dampening mechanisms explored in the study could prove useful in countering autoimmune disorders, during which the immune system is inappropriately activated.

Although the experiments were conducted in mice, the problem of T-cell exhaustion has been identified in HIV, hepatitis B, and hepatitis C infections in humans, according to the report published in the Oct. 18, 2007, issue of *Immunity*.

Using a technique called gene-expression profiling, researchers identified 490 genes whose activity in T cells is altered during a chronic viral infection. Closer study at different time points using a 22-gene subset of the larger group of genes provided molecular signatures of progressive T-cell exhaustion.

At the end of two months, T cells contending with a chronic infection

were sluggish metabolically and immunologically unresponsive to stimulus.

HBV That Can Resist Lamivudine Can Also Resist Entecavir

Researchers, reporting in the *Journal of Medical Virology*, have discovered that similarly-located viral mutations that allow HBV to resist or keep replicating despite treatment with the antiviral lamivudine can also resist the antiviral entecavir (Baraclude).

The researchers discovered an entecavir-resistant strain of HBV, which emerged after prolonged entecavir therapy in a patient who had also not responded to lamivudine. When they analyzed the molecular make-up of the patient's entecavir-resistant HBV, they found amino acid mutations in the same place as where lamivudine mutations occur, which decreased virus' susceptibility to entecavir and lamivudine.

These antivirals

work by interfering with the virus's genetic material to hinder its ability to replicate. Adefovir, they found, was effective against the entecavir-resistant HBV.

HBV Genotypes Dictate Mutations and Susceptibility to Antiviral Resistance

Researchers investigated the genetic differences in HBV from 53 lamivudine-resistant patients with either genotype B or C.

Reporting in the November 2007 issue of the *Journal of Viral Hepatitis*, they found lamivudine-resistant HBV more common in genotype C than genotype B patients (58.5% vs. 41.50% respectively). The occurrence of reverse transcriptase rt204I mutants was lower in genotype B (36.36%) than that in genotype C (87.10%), whereas rt204V mutants were higher in genotype B (63.64%) than that in genotype C (12.90%). The occurrence of precore mutation (nt1896A) was higher in genotype B (77.27%) than that in

genotype C (32.26%). HBV DNA levels were higher in genotype C.

Short-Term HBIG and Long-Term Lamivudine Prevent HBV Recurrence in Transplant Patients

Long-term treatment with the antiviral lamivudine (EpiVir-HBV) combined with hepatitis B immune globulin (HBIG-antibodies) is used to prevent recurrence of hepatitis B virus after liver transplantation. However, HBIG is very costly, so a team of Spanish researchers tried treating 20 transplant patients with just one treatment of HBIG, followed by long-term lamivudine treatment. A control group of nine patients received HBIG and lamivudine indefinitely.

The survival rate was 90% after a follow-up of 83 months. Both groups had similar HBV recurrence rates, 15% for the combination and 11% for lamivudine alone.

Researchers concluded in the September 2007 issue of the journal

Transplantation, “Patients who adhere to long-term prophylaxis (preventive treatment) with lamivudine after early withdrawal of HBIG have a low risk of HBV recurrence, similar to those who receive combination prophylaxis.”

Older Americans Make Up Greater Proportion of HBV-Infected Adults

Older patients make up a growing number of HBV-infected adults, and more of them report they’ve had multiple sex partners, which may have contributed to their infection, according to a report presented to the Infectious Diseases Society of America meeting in San Diego in October 2007.

From 1995 through 2005, the number of HBV patients age 50 and older increased from 13.5% to 21%—a 56% increase.

This increase underscores the need for doctors to take a thorough sexual history of each patient, regardless of his or her age. Older adults should also be made aware that an effective vaccine is available to prevent hepatitis B in those at increased risk.

Experimental HBV Vaccine More Effective in Older Adults

A vaccine created from HBsAg, which is linked to an immune stimulant, proved to be effective in protecting older adults from HBV, according to a report on a Phase III trial presented to the Infectious Diseases Society conference. Older adults tend not to respond to available HBV vaccines and develop the antibodies needed for protection.

The vaccine, developed by Dynavax Technologies, conferred protective antibody protection in 100% of adults, ages 56 to 70, who were immunized. In contrast, only 56% of those adults would have adequate antibody protection if immunized with the standard vaccine.

Researchers reported that 97% of patients who received the investigational vaccine quickly achieved protection by week 12, 99% by week 24, and 100% at weeks 28 and 50. In contrast, the conventional three-dose vaccine achieves seroprotection in 23%, 25%, 73%, and 69% of older patients at the same intervals.

Experimental Blood Test Could Lead to Early Detection of Liver Cancer

Hong Kong researchers unveiled a new blood test that could detect early development of liver cancer and predict how well a patient will do following treatment at the American Association for Cancer Research’ Second International Conference on Molecular Diagnostics in Cancer Therapeutic Development in Atlanta.

Researchers identified an altered version of RASSF1A, a tumor-suppressing gene, in the blood of liver cancer patients and in 58% of HBV-infected people. Healthy subjects showed no signs of the altered gene. They also found that patients who were treated for liver cancer and had high blood levels of this gene were more likely to have a relapse of the disease.

Currently, ultrasound and CT scans are the gold standard for detecting liver cancer, however they are costly. About 70% of patients exhibit a detectable increase in alpha fetoprotein (AFP) through a blood test, but this screen misses many potential patients.

The DNA of liver can-

cer tumor cells lacks a functioning copy of RASSF1A. Researchers matched 63 pairs of patients, one with liver cancer and the other with chronic hepatitis B by age and sex, along with 30 healthy volunteers. They detected RASSF1A in 93% of the cancer patients, 58% of the HBV carriers, and none of the healthy patients. The median RASSF1A levels among cancer patients were 770 copies per milliliter and 118 copies per milliliter for HBV carriers.

In a second study, researchers looked at 22 pairs of gender- and age-matched patients enrolled in a liver cancer-monitoring program involving 1,018 HBV carriers. In the 22 HBV carriers who subsequently developed cancer, there was a significant increase in circulating RASSF1A levels from the time of enrollment to the time of cancer diagnosis. In contrast, there was no significant change in RASSF1A levels over the same period for the 22 matched subjects enrolled in the same program who didn’t develop cancer.

Mixing Large Doses of Acetaminophen and Caffeine May Increase Risk

of Liver Damage

Consuming large amounts of caffeine while taking the over-the-counter pain killer acetaminophen (Tylenol), could potentially cause liver damage, according to a preliminary study reported in the Oct. 15, 2007, issue of the journal *Chemical Research in Toxicology*.

The toxic interaction could occur not only from drinking caffeinated beverages while taking the painkiller but also from using large amounts of medications that intentionally combine caffeine and acetaminophen to treat migraine headaches, menstrual cramps and other conditions.

Health experts have warned against mixing alcohol and acetaminophen, but this is the first time scientists have reported a potentially harmful interaction while taking the painkiller with caffeine, the researchers say.

While the studies are preliminary findings conducted in bacteria and laboratory animals, they suggest that consumers may want to limit caffeine intake, such as energy drinks and coffee, while taking acetaminophen.

Researchers found that

caffeine triples the amount of a toxic by-product, N-acetyl-p-benzoquinone imine (NAPQI), that the enzyme produces while breaking down acetaminophen. This same toxin is responsible for liver damage and failure in toxic alcohol-acetaminophen interactions, they say.

At risk groups includes people with liver damage from viral hepatitis, and those who take certain anti-epileptic medications, including carbamazepine and phenobarbital, and those who take St. John's Wort, a popular herbal supplement.

Fatigue and Loss of Appetite Leads Symptoms Among Americans with Hepatitis B

A survey of symptoms among 258 Americans with chronic hepatitis B identified fatigue and loss of energy (90%) and loss of appetite (79%) as the most common symptoms shared, according to a report published in the October 2007 issue of the *Journal of Viral Hepatitis*.

Of those surveyed, 57% were male and non-Asian, though HBV infections are more preva-

lent among Asian-Americans. About half were Caucasian and one-third were African-American. Most had known about their infections for at least five years.

Non-Asian patients described greater impact from their symptoms, and were more likely than Asian-Americans to consider hepatitis B an overriding concern in their daily activities.

Researchers concluded that HBV-infected patients, "may have greater symptomatology than recognized."

"Additional research about chronic hepatitis B (CHB) symptomatology and health attitudes by ethnicity is needed to ensure that individuals with CHB are educated on the potential health risks and the availability of current treatment options," they wrote.

Hispanic-Americans Have Liver Cancer Second-Only to Asian-Americans

Hispanic-Americans have high rates of liver cancer, second-only to Asian-Americans, according to a report in the October 2007 issue of the *Archives of Internal Medicine*.

Researchers used data from 13 cancer registries in the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute to calculate race-specific, age-adjusted incidence rates between 1992 and 2002, and California and Texas state death records from 1979 and 2001 to calculate race-specific, death rates for liver cancer. Liver cancer rates were higher by 1.2-fold in Hispanics than in African-Americans (6.3 vs. 5.0 per 100,000 person-years) and by 2.7-fold than in non-Hispanic whites, but lower than in Asians/Pacific Islanders (10.8 per 100,000 person-years).

The average age of liver cancer diagnosis in Hispanics was 64. Between 1992-1995 and 2000-2002, there was a 31% increase in the incidence of liver cancer in Hispanic men and a 63% increase in Hispanic women. The race-specific, age-adjusted death rates were remarkably similar in California and Texas and were highest in immigrant Asian/Pacific Islanders followed by native Hispanics.

