Liver disease: Current perspectives on medical and dental management

Keerthi Golla, DMD, a Joel B. Epstein, DMD, MSD, FRCD(C), b and Robert J. Cabay, MD, DDS, c Chicago, Ill
UNIVERSITY OF ILLINOIS AT CHICAGO

The liver has many essential functions, and liver disease presents a number of concerns for the delivery of medical and dental care. A number of conditions that cause liver dysfunction may be related to lifestyle and a variety of diseases. The purpose of this paper is to update dental providers regarding recent progress in liver disease research and to identify ways of caring effectively for patients with hepatic dysfunction. A

Medline search from 1996-2003 was conducted using the following search terms: liver disease, hepatitis, autoimmune hepatitis, fulminant hepatitis, hemochromatosis, liver cirrhosis, and hepatic carcinoma. This update will focus on hepatitis, hemochromatosis, hepatic cirrhosis, hepatocellular carcinoma, and their characteristics pertinent to dental patient management.

HEPATITIS

Hepatitis has a number of potential causes, both infectious and non-infectious. Alcohol, prescription medications, and drug abuse are predominant non-infectious causes, while viruses and bacteria are important infectious etiologic factors. Viral and drug-induced hepatitis are examples of primary hepatitis. Secondary hepatitis may occur as a sequela of other disease entities such as mononucleosis, syphilis, and tuberculosis.1

Hepatitis A

Hepatitis A is caused by the Hepatitis A virus (HAV), an enterovirus of the Picornaviridae family. HAV is

a Senior Resident, General Practice Residency, Department of Oral Medicine and Diagnostic Sciences, College of Dentistry, University of Illinois at Chicago, Chicago, Ill.
b Professor and Head, Department of Oral Medicine and Diagnostic Sciences, College of Dentistry; Director, Interdisciplinary Program in Oral Cancer, College of Medicine, Chicago Cancer Center; University of Illinois at Chicago.
c Resident Physician, Department of Pathology, College of Medicine, University of Illinois at Chicago.

Received for publication Feb 20, 2004; returned for revision Aug 24, 2004; accepted for publication Sep 21, 2004.
1079-2104/5 - see front matter
© 2004 Elsevier Inc. All rights reserved.
Hepatitis B

Hepatitis B virus (HBV) is a DNA virus with a nuclear capsule enveloped by an outer lipid layer containing hepatitis B surface antigen (HBsAg). The nuclear capsule contains other viral components, including the hepatitis B core antigen (HbcAg), the e antigen (HBeAg), DNA, and DNA polymerase. HBV replicates within the hepatocyte through an intermediate step of reverse transcription mediated by viral polymerase.

Sexual contact, intravenous drug use, and transfusion of blood and blood products are common modes of transmission. In Asia, HBV is commonly transmitted perinatally. Transmission via saliva may be important to dentistry, as HBsAg is detectable in saliva of infected individuals. Health care workers, particularly dentists, have three to five times the rate of HBV infection compared to the general population.

Diagnosis of hepatitis B is made by assessing HBV DNA, HBsAg, and e antigen/antibody levels. The symptoms of hepatitis due to HBV are similar to those of hepatitis A. A younger individual who becomes infected with HBV has a higher risk for developing chronic HBV and hepatocellular carcinoma. Approximately 90% of adult HBV-infected patients experience a full recovery, but 5-10% of the patients will develop chronic hepatitis with complications such as cirrhosis and hepatocellular carcinoma.

There are two vaccines available for HBV immunization that utilize recombinant DNA technology, Engerix-B® (Merck) and Recombivax® (Glaxosmith Kline). HBV vaccine is given in three doses over a six-month period and produces an effective antibody response in the majority of individuals. If a nonimmunized individual has a documented exposure to HBV, hepatitis B immune globulin can be provided and may offer postexposure protection. Current guidelines call for HBV immunization as part of a childhood vaccination series.

The steps of HBV replication provide therapeutic targets for antiviral therapy. Nucleoside analogues interfere with viral DNA synthesis by blocking further synthesis when incorporated into viral DNA and/or competitively inhibiting viral polymerase. Current protocols for treatment of HBV infection use interferon and nucleoside analogues such as lamivudine. Other nucleosides with activity against hepatitis B currently being used are famciclovir and adefovir.

Hepatitis C

Hepatitis C virus (HCV) is a blood-borne, single-stranded RNA flavivirus encoding for a capsid protein, two envelope proteins, and some nonstructural proteins. People at increased risk include hemophiliacs, dialysis patients, and intravenous drug users, although transmission is now reduced due to blood and blood product screening. Other modes of transmission are sexual, perinatal, and idiopathic. Though the primary mode of transmission is through blood, HCV has also been detected in saliva. The main diagnostic test for HCV is the enzyme-linked immunosorbent assay (ELISA) for anti-HCV and RT-PCR; ELISA does not distinguish between exposure and infection, whereas RT-PCR can make this distinction.

Eighty-five percent of patients with HCV will develop chronic hepatitis. Chronic HCV infection is the major cause of cirrhosis and hepatocellular carcinoma. Acute HCV infection usually presents with mild flu-like symptoms, while chronic disease is variable in presentation. Patients may experience nonspecific symptoms such as fatigue, nausea, and/or abdominal pain. Chronic HCV infection is normally a slow, progressive disease that may produce few or no symptoms for many years after infection. Some patients develop chronic infection and suffer no significant liver damage, while others progress quickly to liver cirrhosis and may develop hepatocellular carcinoma.
Hepatitis C

Hepatitis C virus (HCV) is a single-stranded positive-sense RNA virus that is highly unstable due to the lack of a lipid membrane. Transmission, similar to HAV, is by the oral-fecal route. The primary method of spread is through contaminated drinking water and occurs mostly in places with inadequate sanitary precautions.

Symptoms of disease commonly include malaise, nausea, abdominal pain, and/or fever. The infection is usually self-limiting, although there have been cases of fulminant hepatitis and chronic disease. In pregnant patients infected with HEV, there is a higher risk of fulminant hepatitis. There is no HEV vaccine available, and treatment is palliative.

Hepatitis G virus (HGV) is caused by two isolated viruses that appear to be almost identical. They are single-stranded, positive-sense RNA viruses similar to HCV. HGV is transmitted through blood and blood products, sexual activity, and perinatal contact. Due to similar transmission routes, HGV may be found in association with other hepatitis viruses, especially HCV. Individuals at risk are organ transplant and blood transfusion recipients, IV drug users, dialysis patients, and health care workers with exposure to blood and chronic HCV patients. Diagnosis is based on detection of HGV RNA in serum one to four weeks after infection. Serum anti-HGV indicates past infection. Although the rate of remission is low, little evidence exists that HGV causes significant liver damage, even with persistent viremia.

Autoimmune hepatitis

Autoimmune hepatitis is a chronic inflammatory disease. Although the etiology is not clear, it is thought that environmental and viral factors may cause alterations in cellular markers on hepatocytes leading to an autoimmune response in genetically susceptible individuals. The etiology appears to be related to antigen-specific and generalized suppressor defects that perpetuate the autoimmune response. The main finding in autoimmune hepatitis is IgG hypergammaglobulinemia, which may be due to chronic infections or alteration in immune response. Autoimmune hepatitis may lead to liver cirrhosis and the treatment of choice is liver transplantation.

Fulminant hepatitis

Fulminant hepatitis is sudden, severe liver dysfunction which may lead to hepatocellular necrosis as well as hepatic encephalopathy. Signs of fulminant hepatitis include jaundice, hepatomegaly, and right upper quadrant tenderness during the inflammatory stage. As necrosis occurs and progresses, the liver becomes atrophic and less readily palpable. With the onset of severe liver failure, liver enzymes, bilirubin, prothrombin time, and partial thromboplastin time will be elevated, while hemoglobin and hematocrit will decrease. The prognosis for fulminant hepatitis is poor, and the treatment of choice is liver transplantation.
HEMOCHROMATOSIS

Hereditary hemochromatosis is a disease in which there is a defect in iron metabolism resulting in malabsorption and iron deposits in the liver, pancreas, heart, kidneys, and other organs. The iron accumulation may lead to diabetes mellitus, cardiomyopathy, and cirrhosis. Mutations in the HFE gene have been proven to be the source of the defect in iron metabolism in 80% of patients. Patients may also present with hemoptoic and hyperpigmentation (especially in the face, neck, forearms, and legs). The severity is affected by genetic and environmental factors, such as iron intake, blood donation, and physiologic blood loss. Women tend to be affected at a later age than men.

An association has been identified between hemochromatosis and hepatocellular carcinoma, especially in patients with both hemochromatosis and liver cirrhosis. In patients with hemochromatosis, the subsequent development of hepatocellular carcinoma is significantly associated with iron-free foci on biopsy.

Once the diagnosis of hepatocellular carcinoma is made and the presence of the C282Y gene established, screening of siblings is indicated. Family members with C282Y homozygosity should be checked for serum transferrin saturation in addition to ferritin and liver enzyme levels. If transferrin saturation is greater than 45% and verified by a second fasting sample, further investigation is warranted.

Once the diagnosis of hemochromatosis has been made, patients should be prescribed a course of iron depletion therapy and monitoring. Therapeutic and maintenance phlebotomy may be performed with regular monitoring of hemoglobin, hematocrit, and serum ferritin levels. Patients with hemochromatosis should avoid iron supplements and abstain from alcohol if liver abnormalities are present.

HEPATIC CIRRHOSIS

Hepatic fibrosis and its end stage, cirrhosis, are an increasing worldwide concern. Cirrhosis is the irreversible end result of fibrous scarring and normal hepatic architecture is replaced with interconnecting bands of fibrous tissue. Normal function is disturbed by the resulting inadequate blood flow and ongoing damage to hepatocytes. The most common etiologic factors resulting in cirrhosis are hepatitis B, hepatitis C, and excessive alcohol consumption. Other potential causative factors are immune-mediated damage, genetic abnormalities, and nonalcoholic steatohepatitis (NASH). Liver fibrosis and cirrhosis are diseases marked by an increase in total liver collagen, as well as other matrix proteins that are disruptive to liver architecture and function.

The major complications of cirrhosis are portal hypertension, hepatocellular carcinoma, and loss of function. Portal hypertension may result in variceal hemorrhage, ascites, and hepatic encephalopathy. Hemorrhage, most commonly from varices in the esophagus, is a severe complication of portal hypertension. Cirrhosis and hepatic encephalopathy may occur due to inadequate hepatic removal of nitrogenous compounds and other toxins.

The path to fibrosis and cirrhosis is mediated by hepatic stellate cells. In the normal liver, stellate cells store retinoids and are present in the spaces of Disse. After injury, the stellate cells become myofibroblast-like and express contractile protein. The stellate cells proliferate and become the major source of the fibrillar collagens that characterize fibrosis and cirrhosis. In areas of injury, cytokines are released by inflammatory cells and activate the stellate cells. Due to the role of inflammation in stellate cell activation, studies of interleukin-10 as a down-regulator of response and tumor necrosis factor alpha as a pro-inflammatory mediator may be valuable clinically for hepatitis C treatment. Other areas of investigation involve the mediators of the fibrogenic reaction of stellate cells such as transforming growth factor beta one, a cytokine that is also involved in fibrosis of other organs, such as the lung and kidney. Signaling through soluble mediators such as transforming growth factor beta is key to the fibrogenic response. By modifying the secretion and/or activity of the aforementioned factors, fibrosis may be prevented.

Current treatment for patients with cirrhosis includes removing the injury-causing stimulus, antiviral therapy, and liver transplantation. For end-stage cirrhosis, transplantation is a highly successful treatment with a high survival rate. However, due to the increased demand, limited availability of organs, compatibility issues, as well as other factors, this option is not for all patients. Alternate treatments are being sought and studied, including antifibrotic therapy.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma is the most common primary cancer of the liver, the sixth most common cancer in men, and the eleventh most common cancer in women in the United States. This cancer is a devastating disease with five-year survival rates around 2%. The most common etiologic factors in hepatocellular carcinoma are HBV and HCV. In this condition, alpha fetoprotein levels may be elevated. The incidence of hepatocellular carcinoma is rising, and this trend is expected to continue for years.

The primary treatment for hepatocellular carcinoma is surgery if the tumor is resectable. Unfortunately, many patients have unresectable cancers due to the
ORAL MANIFESTATIONS

The oral cavity may show evidence of liver dysfunction with the presence of hemorrhagic changes, petechiae, hematoma, jaundiced mucosal tissues, gingival bleeding, and/or icteric mucosal changes. HCV has been linked to the onset. Sjögren’s syndrome and chronic hepatitis have been associated with lichen planus in some studies. Glossitis may be seen with alcoholic hepatitis, especially if combined with nutritional deficiencies. Ecchymosis and reduced healing after surgery may also be identified. In some cases, parotid gland enlargement is evident. These oral changes often appear in combination with general signs and symptoms of liver disease such as fatigue, malaise, confusion, weight loss, nausea, vomiting, hepatomegaly, hemorrhagic changes, spider angiomas, edema, ascites, dark urine, and pale/clay-colored stool.

DENTAL MANAGEMENT

Disorders of the liver have many implications for a patient receiving dental treatment (Table I). Dental care providers should be aware of the potential for increased bleeding as well as drug toxicity. Thorough medical and dental histories are essential, including questions regarding hepatitis, jaundice, cancer, autoimmune disorders, HIV/AIDS, surgeries, family history, medications, alcohol intake, recreational drug use, sexual history, and bleeding tendencies. It is prudent to discuss the details of the liver disease with a treating physician in order to provide the patient with a dental treatment plan that is safe and appropriate for the medical and dental conditions with which the patient presents.

Quite often, liver disease will result in depressed plasma levels of coagulation factors that need a careful evaluation of hemostasis prior to treatment. Patient testing should include CBC, PT, PTT, INR, bleeding time, and liver function tests. If any abnormal levels are discovered, consultation with a hematologist or hepatologist is suggested before beginning dental treatment. If oral surgical procedures are required, special attention should be paid to the minimization of trauma to the patient. As the risk of bleeding increases, an infusion of fresh frozen plasma may be indicated. Advanced oral surgical procedures or any dental procedures with the potential to cause bleeding performed on a patient with multiple or a severe single coagulopathy may need to be provided in a hospital setting.

Certain sedatives (diazepam, barbiturates) and general anesthetics (halothane) impair detoxification in hepatic disease and should be used cautiously. Brain metabolism may be altered, and sensitivity to medications may increase. Encephalopathy can be triggered by sedatives and opioids. Caution should be used in prescribing medications metabolized in the liver, such as methyldopa, isoniazid, nitrofurantoin, aminophen, nonsteroidal anti-inflammatory agents, phenytoin, phenobarbital, valproic acid, and some sulfonamides.

Local anesthetics should be administered cautiously to patients with hepatic impairment. Most amides are primarily metabolized in the liver and therefore may reach toxic levels with lower doses of anesthetic. Articaine (plasma) and prilocaine (partly in lungs), however, have other sites of metabolism. Drug dosages and possible interactions should be discussed with a treating physician. In some cases, lower drug dosages are required, while some drugs (erythromycin, metronidazole, tetracyclines) should be avoided completely. Nonsteroidal anti-inflammatory agents should be used cautiously or avoided due to an increased risk of...
gastrointestinal bleeding and interference with fluid balance. Prophylaxis with an antacid or histamine receptor antagonist may be considered to prevent gastritis and gastrointestinal bleeding associated with the hepatic dysfunction. Any modifications in medication regimen should be made in conjunction with the suggestions of a treating physician.

REFERENCES