CIRRHOSIS

The major significance of chronic hepatitis is its possible progression to cirrhosis, an end stage of the process of scarring and regeneration of the liver in response to chronic damage. The scarring causes increased resistance to blood flow through the portal vein (carrying blood from the intestine to the liver), leading to ascites, esophageal varices, and increased risk of infection. Eventually, cirrhosis can cause liver failure, and is the major cause for liver transplantation. Currently, the "gold standard" for evaluation of patients with chronic hepatitis is liver biopsy, which allows determination of the severity of damage.

Chronic hepatitis has two major components: inflammatory damage and fibrosis. While the extent of inflammation reflects the degree of damage at that point in time, the extent of fibrosis more closely relates to likelihood of developing cirrhosis. Plasma activities of aminotransferases are not related to degree of fibrosis, and there is at best a weak correlation between plasma ALT activity (290, 291) or (in chronic HCV) HCV RNA levels (291) and histological activity. At best, ALT explains only 30-50% of variation in histologic activity, and there is considerable overlap in values in patients with mild, moderate, or severe activity (290, 291). The activity of inflammation has weak correlation with rate of progression of fibrosis. (292)

Liver fibrosis is associated with deposition of a number of proteins in the liver. Among the proteins produced as part of fibrosis are collagen, laminin, elastin, and fibronectin; and enzymes produced in collagen synthesis such as lysyl- and proline hydroxylase. Varioius proteoglycans, such as hyaluronate, are also produced in the process of fibrosis. Fibrosis is removed by a variety of related enzymes, termed matrix metalloproteinases; these enzymes and their inhibitors are also produced in chronic hepatitis. Numerous studies of plasma levels of proteoglycans, proteins of fibrosis, and their precursors (293, 294) have shown at best a weak correlation between marker levels and extent of fibrosis. Levels reflect degree of fibrogenesis at the time of sampling, and there is considerable overlap in values with varying degrees of fibrosis.

In the process of progression from chronic hepatitis to cirrhosis, a number of changes occur in basic laboratory test results. Several studies have shown that the ratio of AST to ALT is typically < 1 in patients with chronic hepatitis (except that due to alcohol), but with progression to cirrhosis the ratio often increases to > 1: the specificity of a ratio > 1 is 75-100%, with sensitivity 32-83%. (100, 220) In one study (220), the ratio also increased with increasing fibrosis score. This appears to be due to a reduction of ALT production in damaged liver. (295) Other routine tests that predict likelihood of cirrhosis are thrombocytopenia and prolonged prothrombin time; an index using these two variables with AST/ALT ratio has a sensitivity of 46% and specificity of 98% for cirrhosis (100). Albumin is commonly measured in patients suspected of progressing to cirrhosis. While it is not as sensitive as other markers, it is used as a marker of severity as part of the Child-Pugh classification of cirrhosis. AFP is more likely to be elevated as degree of hepatic fibrosis increases (296), especially in cirrhosis;

AFP greater than 17.8 ng/mL has a sensitivity of 35%, specificity of 98.6%, and positive predictive value of 97.7% for cirrhosis. (297)

Recommendations

Biopsy is the only definitive marker of progression from chronic hepatitis to cirrhosis (IIB).

Laboratory markers of fibrosis should not be used except in research studies (IIIB, E).

Markers of hepatic function that may indicate progression to cirrhosis (AST/ALT ratio, albumin, prothrombin time, platelet count) should be measured every 3-6 months in patients with chronic hepatitis (IIIB).