Serum Proteins in Hepatic Disease

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ABSTRACT

The serum protein changes occurring in liver disease associated with parenchymal damage are characteristically decreased in serum albumin and increased in gamma globulin levels. Beta-gamma bridging in the electrophoretogram is highly characteristic of hepatic cirrhosis. Variation of alpha 1, alpha 2 and beta fractions is inconstant and is not of great diagnostic or prognostic value. The increase in gamma fraction is polyclonal in nature and is due first to increase in IgM fraction followed by an increase in IgG fraction. Elevation of IgA fraction is not as constant or prominent.

The role of the liver in metabolism of body proteins is abundantly illustrated by many observations of clinical as well as research nature. This role may be roughly divided into the following phases: (1) in providing simple precursors from the metabolic pool for synthesis of tissue protein, (2) in formation of hepatic proteins, (3) in synthesis of serum proteins, (4) in storage of proteins, (5) in the catabolic process of breaking down proteins to amino acids, (6) in deamination of amino acids to form urea and (7) additionally in other transformation processes (e.g., transamination) of amino acids. This article deals exclusively with the serum proteins and their changes occurring in diseases of the liver.

Serum Albumin

Albumin is believed to be synthesized solely in the liver. The experimental observation of a sudden and precipitous drop of serum albumin after hepatectomy is confirmed by the constant clinical observation of decrease of serum albumin levels in hepatic diseases associated with destruction or loss of parenchymal elements. In a clinical setting, these changes are slow and do not necessarily immediately reflect acute liver damage. Thus, in a patient with acute viral hepatitis, serum albumin levels may be normal in the early stages of the disease process and may gradually decrease only after parenchymal compromise has occurred. Conversely, in liver diseases in which parenchymal involvement is minimal or absent (e.g., biliary obstruction), serum levels are usually normal. In severe and prolonged viral hepatitis and in cirrhosis, the serum albumin levels bear a close relation to the clinical state and are helpful prognostically and in following results of treatment.

The importance of the integrity of the hepatic parenchymal cell in the synthesis of serum albumin is illustrated by the work of Chey et al, in which hepatic lesions similar to those of alcoholic liver disease in the human were produced by prolonged administration of ethanol to dogs. One of the prominent biochemical changes occurring in these experimental animals was a gradual but progressive decrease in serum albumin despite an adequate dietary intake.
Serum Globulins

Alpha globulins, including alpha 1 antitrypsin, glycoprotein, alpha 2 lipoproteins, alpha 2 macroglobulins, haptoglobin and ceruloplasmin are synthesized in the liver. Some of the beta globulins, including beta lipoproteins, transferrin, hemopexin, are likewise synthesized in the liver. Alpha 1 globulins tend to be low in hepato-cellular disease falling in parallel with the serum albumin. Alpha 2 and beta globulins contain lipoproteins which may be markedly increased in cholestatic lesions of the liver. In cholestasis, the increase in alpha 2 and beta globulin components correlates with the height of serum lipid values and may be a useful point in distinguishing between biliary obstructive lesions and other non-obstructive types of jaundice.

Gamma globulins are commonly markedly increased in chronic hepatic disease and are not formed in the liver primarily but in the cells of the immunoblastic system. The liver assumes only a minor role in this process only to the extent of its content of elements of the reticuloendothelial system (lining sinusoidal cells and Kupffer cells).

Havens presented a study of the proteins in hepatic diseases. Except for gamma globulin, the liver produces most of the plasma proteins including albumin, enzymes, coagulation factors, lipoproteins and glycoproteins. Gamma globulin is produced by the reticuloendothelial cells. Although these reticuloendothelial elements occur in the liver, evidence indicates that in this site their participation in the production of gamma globulin is insignificant under normal conditions.

There is evidence that in certain hepatic diseases gamma globulin may be produced in increasing amounts by the hepatic reticuloendothelial cells. However, the classic pattern of changes in various liver diseases includes increase in gamma and/or beta globulins with or without diminution of albumin. Alpha 1, alpha 2 and beta globulin are slightly decreased in viral hepatitis along with gradual decrease of albumin. Diminution of alpha 2 globulin to low levels may be a poor prognostic sign. The gamma globulin returns to normal late in convalescence. Failure to return to normal should raise a suspicion of delayed recovery or chronic active hepatitis. In cholangiolitic hepatitis, there is an increase in beta globulin which may reach very high levels in chronic progressive disease.

Hepatic Cirrhosis

Sunderman and Sunderman presented data from 95 patients with Laennec's cirrhosis and 18 patients with viral hepatitis. In cirrhosis there was a significant diminution in the mean concentration of albumin and an increase in the mean concentration of gamma globulin while the mean concentration of alpha and beta globulins were normal. They also pointed out the characteristic feature of the electrophoretic pattern in hepatic cirrhosis of beta-gamma bridging, i.e., a lack of demarcation between the peaks of beta and gamma globulins. They indicated that beta-gamma bridging almost always denotes hepatic cirrhosis.

Powell et al studied a series of 400 unselected patients with hepatic cirrhosis admitted to two large hospitals in Australia. Prominent in the biochemical abnormalities were abnormal serum electrophoretic patterns in 78.2 percent of patients with alcoholic cirrhosis, 86 percent of patients with cryptogenic cirrhosis, 96.3 percent with active chronic hepatitis and 56 percent of patients with hemochromatosis. In over 40 percent of patients with alcoholic cirrhosis, there was an abnormal protein band between the beta and gamma globulins (beta-gamma bridging). Serum immunoglobulin levels were measured in 56 patients. Elevated IgG levels were present in about 50 percent of those tested in each type of cirrhosis except hemochromatosis. Twelve of 20 alcoholic patients showed elevated IgG and IgA levels. IgM levels were in-
increased in 14. The frequency of increased levels of IgG, IgA and IgM in patients with alcoholic cirrhosis did not differ significantly from that of patients in other groups.

Murray-Lyon et al3 studied the changes occurring in 10 serum proteins by quantitative IEP in 42 patients with inactive cryptogenic cirrhosis, alcoholic cirrhosis and active chronic hepatitis. Alpha 2 macroglobulins were significantly increased in each group of patients. Alpha 2 glycoproteins, ceruloplasmin and transferrin were elevated in patients with active chronic hepatitis while ceruloplasmin was raised in patients with alcoholic cirrhosis. The only proteins to be significantly reduced were transferrin in alcoholic cirrhosis and haptoglobin in active chronic hepatitis. Other proteins of the alpha1, alpha2 and beta1 groups showed no significant variation from normal. These authors indicated that although there do appear to be distinct differences in the patterns of abnormality found, the correlation between changes in protein concentration of clinical or biochemical assessment of the severity of the disease was poor and not of particular prognostic value.

Viral Hepatitis

Peters and Ashcaval4 studied the immunoglobulin levels in the detection of viral hepatitis in order to determine the usefulness of serum immunoglobulin quantitation in screening for occult viral hepatitis, evaluating the course of viral hepatitis and for distinguishing serum hepatitis from infectious hepatitis. Of the patients studied throughout the course of viral hepatitis, there was a fairly characteristic immunoglobulin response characterized by an initial elevation of IgM level followed by an elevation of IgG levels. However, Peters and Ashcaval considered this response a non-specific response, reflecting only the patient's immunologic reaction to an inflammatory process. They did not consider these tests of sufficient discriminative value as to be reliable in diagnosis.

Summary

In summary, the serum protein changes occurring in liver disease associated with parenchymal damage characteristically are decreased in serum albumin and increased in gamma globulin levels. Beta-gamma bridging in the electrophoretogram is highly characteristic of hepatic cirrhosis. Variation of alpha1, alpha2 and beta fractions is inconstant and is not of great diagnostic or prognostic value. The increase in gamma fraction is polyclonal in nature and is due first to increase in IgM fraction followed by an increase in IgG fraction. Elevation of IgA fraction is not as constant or prominent.

References