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A Review

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The current literature concerning chronic acute hepatitis is reviewed. The clinical picture, morphology, laboratory data and etiology are discussed. It is pointed out that much work is still to be done toward fully understanding this disease. A program of treatment is suggested.

A group of young women with chronic liver disease and hypergammaglobulinemia was described by Kunkel and Ahrens[1] in 1951. In the following years the term chronic active hepatitis[2] (CAH) was applied to this entity. The appearance of LE cells was described in similar groups of patients.[3-4] It was then apparent that many of these patients had systemic clinical features usually not seen in viral hepatitis or cirrhosis. In 1956, Mackay et al[5] introduced the term "lupoid hepatitis" in their description of a group of seven patients and suggested an antigen-antibody reaction was an important etiologic factor in this disease. In a later description Mackay[6] included lupoid hepatitis in a group of 69 patients with CAH and put forth the following characteristics:

1. persistent fluctuating activity for more than six months,
2. activity manifested by elevation of serum transaminases,
3. elevation of serum gamma globulin by 2 to 6 grams,
4. morphologic piecemeal necrosis, lymphoid infiltration and fibrosis,
5. various serum auto-antibody reactions,
6. suppression by immune suppressive drugs in the early stage of the disease.

Because of the variability of the clinical and histological picture, chronic active hepatitis has been described under a variety of names. A few examples are cryptogenic cirrhosis,[7] chronic liver disease in young women,[8] plasma cell hepatitis,[9] progressive hepatitis,[10] active juvenile cirrhosis,[11] subacute hepatitis,[12] and auto-immune hepatitis.[6,26]

Clinical Features

The term chronic active hepatitis includes a heterogenous group of patients with a spectrum of disease varying from viral hepatitis to cirrhosis. However, a past history of viral hepatitis can be obtained in only a small num-

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ber of patients.[13] The age of onset ranges from the first to the seventh decade, but the majority of patients are first seen in their early teens or twenties.[8,9,14] There is a predominance of female over male patients[14,15] and a role for estrogens has been suggested in the pathogenesis of this disease.

Jaundice and insidiously developing fatigue are predominant clinical symptoms,[15] often accompanied by low grade fever, anorexia and malaise. Systemic involvement is frequent. Maclachlan[15] observed arthralgias and arthritis in 16 of a group of 20 patients with CAH. There was involvement of the heart in three and of the lungs in five. Other systemic complications included generalized lymphadenopathy, glomerulonephritis, generalized convulsions, ulcerative colitis, leucopenia, thrombocytopenia, and urticaria. Similar observations were made by other authors.[4,14] The liver is usually firm and tender, and the spleen is frequently enlarged. Spider angiomata are noted with ascites in 30% of observed cases.[15]

Four variants were suggested by Schaffner and Klion,[13] although all are understood to represent the same disease:

1. CAH occurring in postmenopausal women, with a more rapid and progressive course towards cirrhosis and death.
2. CAH in young girls near puberty with associated menstrual abnormalities and a marked sensitivity to estrogens.
3. CAH in prepubertal boys with a more rapidly progressive course than in girls of a similar age group.
4. CAH in young women with a higher incidence of systemic manifestations, including positive LE cell preparations, butterfly rash, pleurisy and hemolytic anemia. This group of patients led to the use of the term "lupoid hepatitis."[5,6] There has been considerable controversy whether these patients constitute a separate entity.[14]

Laboratory Findings

Levels of transaminases usually fluctuate widely,[13] the alkaline phosphatase is generally elevated[15] while the bilirubin may be normal. Schaffner and Klion[13] found it hard to correlate these laboratory data with the clinical picture and the morphology of the liver. Most impressive is the elevation of the gamma globulins,[6,8,12,14,15] apparently with IgG as the main contributor.[16-19] IgM may be moderately increased,[16-19] while measurements of IgA may range from a decreased level[16-18] to a moderate increase.[19] Patients with a positive antinuclear factor tend to have a more significant increase of IgM.

Positive LE preparations and antinuclear factor are found frequently as expressions of nonspecific antigen-antibody reactions. Maclachlan[15] reported positive LE cells in 14 of 19 patients and positive homogenous antinuclear factor in 16 of 18 patients. Mackay and Wood[20] observed positive LE cells in 22 of 72 patients. Mackay et al[6] attempted to separate lupoid hepatitis from CAH. They found 10% positive homogenous antinuclear factor and 30% positive speckled antinuclear factor in chronic active hepatitis. This contrasted with 32% positive homo-

genous and 41% positive speckled antinuclear factor in lupoid hepatitis. False positive serologic tests for syphilis have also been reported.[15]

Specific circulating antibodies against the individual liver cell have never been reported,[6,13] although antibodies directed against proliferating bileduct cells have been observed.[21] Non-organ-specific antibodies directed against mitochondria, present in virtually all patients with primary biliary cirrhosis, were found in 28% of patients with CAH;[22] smooth muscle antibodies were found in 48% of CAH;[23] antibodies to cytoplasmic antigens in 12 of 15 patients.[24]

Pathology

Four pathologic processes take place in chronic active hepatitis, all closely linked, though one might predominate:

1. Necrosis of individual liver cells at the periphery of the liver lobule with subsequent destruction of the limiting end plate.[21] (Electron microscopic changes varying from cell to cell: focal cytoplasmic degeneration, hypertrophy and vesiculation of the endoplasmic reticulum and shedding of the cytoplasm from the sinusoidal surface.[13])

2. Active fibroplasia around damaged liver cells with newly formed capillaries, proliferating bile ducts and septal formation by fibroblasts eventually leading to cirrhosis.[21]

3. Accumulation of mononuclear cells deriving from the reticuloendothelial system after transition through macrophages. These cells contain gammaglobulin, demonstrable by immunofluorescence, and are thought to be the cause of the hypergammaglobulinemia[21,25] (immunocytes).

4. Active regeneration with multinucleation of hepatocytes and nodule formation.

Etiology

The cause of chronic active hepatitis is not known and it is probable that this disease has several etiologic components. Disturbances of hepatic circulation, malnutrition and genetic factors have been considered. Mackay[6,26] believes that CAH represents the result of liver damage caused by viruses in persons with abnormal immune tolerance, particularly those with the tendency to respond abnormally to the release of liver cell compounds. The autoimmune response then is perpetuated because immunocytes continue to be stimulated by antigen from damaged liver cells. Evidence against this theory is the absence of demonstrable antibodies against hepatocytes.[6,13] Popper[27] does not believe in autoimmunity by direct action of circulating antibodies. He suggests that the autoimmune process is initiated by complexes between antibodies and antigens, not necessarily hepatic and that they are responsible for perpetuation of the process. The systemic features, often resembling systemic lupus erythematosis, are caused by the same circulating antigen-antibody complexes. Not understood is the frequent occurrence of CAH leading to cirrhosis in patients with congenital agammaglobulinemia.

Therapy

No specific therapy against CAH is available. Results of therapy are difficult to assess and controlled clinical trials are few in number. It is important to realize that therapy should not be guided by the morphology of liver biopsies nor by laboratory tests, but by the symptoms and clinical appearance of the patient. Immunosuppressive agents (steroids, Azathioprine, 6-Mercaptopurine) will improve BSP excretion[28] and will reduce the gammaglobulin, transaminase, and bilirubin levels.[15,26,30-32] However, this therapy may not delay the inexorable progress of the disease to cirrhosis and death.[31,32]

A suggested course of management[29] includes: Activity and diet directed by the patient's symptoms; complications treated symptomatically in the usual fashion. More severe symptoms may respond to Prednisone, started at 60 mg daily (single dose) and gradually reduced over several months to 10-20 mg daily. If symptoms cannot be controlled, a trial with Azathioprine should be attempted, 50-150 mg daily. Occasionally the combination of 5-10 mg of Prednisone with 25-50 mg of Azathioprine has been beneficial.

Prognosis

The natural history of chronic active hepatitis progresses to the complication of portal hypertension and hypersplenism. The disease course is fluctuating but progressive and many patients die from hepatic failure and from bleeding esophageal varices. Mortality also occurs from associated complications including ulcerative colitis, septicemia, pyelonephritis and glomerulonephritis. The average survival from the time of diagnosis ranges from four to seven years.[6,8] Although the ultimate prognosis of CAH is guarded, an occasional patient maintains symptomatic good health over a long period of time in spite of laboratory evidence of severe liver disease. If the prognosis of CAH is to be more hopeful, fundamental knowledge is necessary in the etiology and pathogenesis of this disease.

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