Chronic active hepatitis at Baragwanath Hospital

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Summary

In a retrospective analysis of 35 Black patients with chronic active hepatitis (CAH) admitted to Baragwanath Hospital, Johannesburg, during the period 1972-1980, four major aetiological categories were found: auto-immune (lupoid, immunological (57%)), drug-induced (isoniazid and α-methyldopa (17%)), heptatitis B virus-related (14%), and alcohol-related (11%) CAH. Alcohol-related CAH was found in males only. Upper abdominal pain was a presenting feature of alcohol-induced CAH, while jaundice was a common presenting feature of the other types. Systemic features such as skin rashes (acne, urticaria), bacterial infections and congestive cardiac failure were prominent in the auto-immune type of CAH. The liver was enlarged in the majority of cases. Hepatitis B virus-related CAH showed an absence of tissue nonspecific auto-antibodies. Cirrhosis was present in approximately 50% of patients at the time of diagnosis. Despite the facts that isoniazid and α-methyldopa are commonly used and hepatitis B infections and alcohol abuse are frequent in this population, CAH remains an uncommon condition in South African Blacks.

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Chronic active hepatitis (CAH) is a liver disease of varied aetiology and variable clinical features. The diagnosis of CAH is essentially pathological and 'the features common to all untreated cases are piecemeal necrosis together with new fibre formation and a lymphocytic infiltration of the portal tracts and lobules ... bridging or multilobular hepatocyte necrosis may be present ... cirrhosis may develop'.[1] CAH may be caused by viruses (hepatitis B virus and non-A, non-B hepatitis viruses), drugs (α-methyldopa, isoniazid, oxyphenisatin, nitrofurantoin, sulphonamides, propylthiouracil, perhexilene maleate, dantrolene sodium, aspirin, halothane), ethyl alcohol abuse, Wilson's disease, ulcerative colitis, Crohn's disease, α_1-antitrypsin deficiency and auto-immune disorders (i.e. lupoid or immunological).

During the period 1972-1980 35 Black patients with CAH were seen at Baragwanath Hospital, Johannesburg. The aetiology and the clinical, biochemical and immunological features of the disease were analysed retrospectively.

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Patients and methods

Patients were only included in the analysis if they satisfied the clinical, biochemical, immunological and, most important, the histological criteria for CAH. In this regard, important points included a history of recurrent jaundice, multisystem disease, evidence of chronic liver disease, a tenfold increase in the serum aspartate aminotransferase (AST) level or a fivefold increase in the AST level and a twofold increase in the serum gammaglobulin level, the presence of nonspecific auto-antibodies such as the lupus erythematosus (LE) cell phenomenon, antinuclear factor (ANF), anti-smooth-muscle antibody (ASMA) and anti-mitochondrial antibody (AMA), evidence of piecemeal necrosis, portal tract infiltration, fibrosis, bridging or multilobular necrosis, cirrhosis and response to steroids. The different aetiological groups are defined as follows: (*i*) auto-immune (lupoid, immunological) CAH — history, clinical examination, including multisystemic involvement and the absence of other aetiological factors; (*ii*) post-hepatitis B and non-A, non-B hepatitis-related CAH — history of blood transfusion(s), serological evidence of hepatitis B virus infection; (*iii*) drug-induced CAH — history of ingestion of a drug, absence of other aetiological factors and regression of the disease following withdrawal of the initiating agent; (*iv*) alcohol-induced CAH — history of alcohol abuse, appropriate clinical features, including Dupuytren's contracture, bilateral parotid enlargement, palmar erythema, spider angiomas, gynaecomastia (in males) and histological features of alcoholic liver disease (steatonecrosis, hepatitis with cell necrosis, polymorph infiltration, Mallory's hyalin and micronodular cirrhosis; (*v*) CAH related to ulcerative colitis and Crohn's disease — clinical and radiological evidence of chronic inflammatory bowel disease; (*vi*) Wilson's disease — family history and past history of chronic liver disease, haemolysis, central nervous system disease, evidence of basal ganglia disease, presence of Kayser-Fleischer rings, low serum ceruloplasmin and raised urinary and hepatic copper levels; and (*vii*) α_1-antitrypsin deficiency-related CAH — history of jaundice during infancy, clinical features of emphysema and periodic acid-Schiff (PAS)-positive globules in the hepatocytes.

A full blood count, measurement of the ESR (Westergren), urea and electrolyte values and prothrombin index, liver function tests (serum bilirubin, AST, alanine aminotransferase, lactic dehydrogenase, alkaline phosphatase, total protein, serum albumin) and LE cell, ANF, ASMA and AMA tests were performed in all patients using standard methods. Hepatitis B surface antigen was determined in the serum of patients by immunodiffusion (8 patients), immuno-electrophoresis (10 patients) and complement fixation (4 patients) — in 12 of these patients all three methods were used — and by reversed passive haemagglutination (13 patients). Percutaneous liver biopsy was performed in all but 1 of the patients.

Results

Data were first analysed according to aetiology (Table I). Only four types of CAH were found: (*i*) auto-immune (lupoid, immunological); (*ii*) hepatitis B virus-related CAH; (*iii*) alcohol-

TABLE I. CHARACTERISTICS OF THE PATIENTS WITH DIFFERENT TYPES OF CAH

	Auto-immune	Drug-induced	Alcohol-related	Hepatitis B virus-related
No. of patients	20	6	4	5
Age range	10 - 60 yrs	21 - 58 yrs	48 - 69 yrs	14 - 59 yrs
Mean age	35 yrs	40 yrs	59 yrs	43 yrs
Sex (F/M)	12/8	4/2	0/4	1/4
Presenting features	Recurrent jaundice 12 (60%) Epistaxis 1 (5%)	Jaundice 6 (100%)	Upper abdominal pain 4 (100%)	Jaundice 4 (80%) Neurological 1 (20%)
Symptoms	Abdominal pain 4 (20%) Heart failure 3 (15%) Rash 8 (40%) Arthritis 1 (5%) Bleeding 1 (5%) Ascites 4 (20%)	Abdominal pain 2 (33%)	Jaundice 1 (25%) Abdominal swelling 2 (50%)	
Signs	Hepatomegaly 20 (100%) Splenomegaly 10 (50%) Jaundice 13 (65%) Ascites 4 (20%) Oedema 2 (10%) Acne/urticaria 8 (40%) Asthma 2 (10%) Cardiac failure 3 (15%) Infection 3 (15%) Fibrosing alveolitis 1 (5%)	Hepatomegaly 6 (100%) Jaundice 6 (100%) Acne 5 (83%) Confusion 2 (33%)	Hepatomegaly 3 (75%) Jaundice 1 (25%) Oedema 2 (50%) Infection 1 (25%)	Hepatomegaly 5 (100%) Splenomegaly 2 (40%) Jaundice 4 (80%) Ascites 1 (20%) Oedema 1 (20%)

related CAH; and (*iv*) drug-induced CAH. The commonest type was auto-immune CAH (20 patients). This was followed by drug-induced CAH (6 patients), the drugs being isoniazid (5 patients) and α-methyldopa (1 patient). The next commonest type was hepatitis B virus-related CAH (5 patients). Alcohol-related CAH was found in only 4 patients, who had been ingesting alcohol for periods ranging from 2 months to 2 years (mean 7,5 months). Alcohol-related CAH occurs in an older age group than do the other types of CAH, and predominantly in males, unlike auto-immune and drug-induced CAH.

Presenting features, symptoms and signs

Jaundice was a common presenting feature in patients with auto-immune, drug-induced and hepatitis B virus-related CAH. The presenting feature in all patients in the alcohol-related CAH group was upper abdominal pain. Epistaxis due to severe thrombocytopenia was the presenting feature in 1 patient with auto-immune CAH. In the hepatitis B virus-related CAH group 2 patients presented with hepatic encephalopathy while 1 was admitted with bilateral pyramidal tract signs.

Cardiac failure was present in 3 patients with auto-immune CAH, the causes being severe aortic stenosis (1 patient), probable rheumatic mitral regurgitation (1 patient) and a mitral subvalvular left ventricular aneurysm (1 patient). Facial acne (10 patients) was a prominent feature in the auto-immune and drug-induced groups, which also shared other clinical, biochemical and immunological features. A patient with auto-immune CAH developed cutaneous vasculitis, fibrosing alveolitis and arthritis. Infections such as abscesses (2 patients) and bacterial pneumonia (2 patients) were common in the auto-immune group.

Liver function

Overall liver function tests showed that the patients had moderately active chronic liver disease. Tissue nonspecific auto-antibodies were absent in the hepatitis B-related CAH group.

Cirrhosis was present in approximately 50% of the patients at the time of diagnosis.

Cause of death

A total of 7 patients died. In patients with lupoid CAH death was caused by liver failure (1 patient), bacterial peritonitis (1 patient), and intra-abdominal haemorrhage following percu-

taneous liver biopsy performed under platelet cover in a patient with thrombocytopenia (1 patient). Hepatocellular carcinoma (1 patient) and botryomycosis (1 patient) were the causes of death in the alcohol-related CAH group. In the drug-induced CAH group 1 patient died from variceal haemorrhage, and carcinoma of the oesophagus was responsible for the death of 1 patient in the hepatitis B virus-related CAH group.

Follow-up

A total of 24 patients were lost to follow-up and some were followed up for a short period only. All but 1 patient in the drug-induced CAH group responded to withdrawal of the incriminating drug. Of the patients in whom long-term follow-up was possible, 4 with auto-immune CAH were initially treated with glucocorticoids and responded well to treatment. They are now not receiving treatment because their disease is inactive and they are well 5 years after diagnosis.

Discussion

In this retrospective study of CAH at Baragwanath Hospital certain interesting features emerged. The common drugs implicated in our series were isoniazid and α-methyldopa. Goldstein *et al.*[2] found a drug aetiology in 67% of patients with histological criteria of CAH, the drugs implicated being oxyphenisatin (9 patients) and methyldopa (5 patients). A variable period of drug ingestion may produce CAH, the periods varying from 2 months to as long as 3 years. Drug-induced CAH is an important entity to recognize, since clinical improvement or lack of progress of the liver disease occurs after withdrawal of the incriminating drug. If no response to the withdrawal of the drug occurs, glucocorticoids should be used. Clinically, biochemically, immunologically and histologically, drug-induced CAH may be similar to auto-immune CAH.[3] It is not clear whether the drugs precipitate CAH in susceptible individuals.

In the UK and Australia the commonest type is the auto-immune CAH, and females are most frequently affected. Our studies show a fairly even sex distribution, as do the series reported from Zimbabwe[4] and Cape Town.[5] However, in the former series auto-immune phenomena were absent. A proportion of these were possibly hepatitis B-related. Of our patients 37% developed jaundice within a 3-month period.

Prednisolone alone or a small dose of prednisolone combined with azathioprine are the drugs of choice for treatment of lupoid hepatitis.[6] Total (i.e. clinical, biochemical and histological) remission can be expected in 56% of patients with severe disease after a mean of 21 months of treatment.[7]

Prednisolone significantly improves survival, especially in the first 5 years of therapy.[8] In these years death usually results from hepatocellular failure, which becomes uncommon later. Spontaneous remission can also occur in 20% of patients with severe disease, in which the natural history is progression to inactive macronodular cirrhosis.[8]

Hepatitis B virus-related disease is the commonest cause of CAH in the Mediterranean littoral, the Middle East and Asia. Hepatitis B virus-related CAH typically affects elderly males. Auto-antibodies are typically absent, as in our series, and hyperglobulinaemia is rare. The response to steroids is uncertain. Several studies show that patients in this group respond poorly to glucocorticoids.[9] Antiviral agents would be a rational form of treatment.

At present no definitive test is available for the detection of hepatitis non-A, non-B virus(es), so that this group of CAH cannot be completely excluded. Serum ceruloplasmin values in our patients were normal. There was no clinical, radiological or biochemical evidence of chronic inflammatory bowel disease or α_1-antitrypsin deficiency. These are all rare causes of CAH.

Many of the precipitating causes of CAH are common in our Black population. Hepatitis B infections are common and the carrier rate in urban Blacks is 4% (M. C. Kew, G. Macnab — unpublished data). Tuberculosis is rife and isoniazid remains the most commonly used drug. Hypertension occurs in up to 33% of urban Blacks in the 4th decade,[10] and α-methyldopa is frequently used. Alcohol abuse is the commonest social problem encountered.

An increasing awareness of the condition may result in its being diagnosed more frequently, but despite the fact that risk factors are common in urban Blacks, CAH remains a rare condition. A possible explanation for this anomaly is that the condition is missed or that patients, who are largely asymptomatic, do not attend for treatment. The natural history of the disease suggests that many of these patients would eventually present with cryptogenic cirrhosis. This condition is, however, uncommon in our experience at Baragwanath Hospital. An alternative explanation is that this population is not susceptible to CAH, and further studies are indicated.

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