Contrasting features and responses to treatment of severe chronic active liver disease with and without hepatitis B\textsubscript{s} antigen\textsuperscript{1}

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SUMMARY To determine the clinical implications of HB\textsubscript{s}Ag in severe chronic active liver disease (CALD), patients with HB\textsubscript{s}Ag positive CALD were compared with those chosen by identical clinical, functional, and morphological criteria in whom this test and anti-HB\textsubscript{s} were negative. HB\textsubscript{s}Ag positive patients were predominantly males over 40 years of age and more frequently failed to respond to conventional treatment programmes with prednisone. HB\textsubscript{s}Ag negative patients were more often female and younger, had a higher incidence of associated immunopathic disease and immunoserological markers in high titre, and more often responded to treatment with full remission of their disease. HB\textsubscript{s}Ag positive patients failing treatment with conventional doses of prednisone often improved with higher doses, but did not reach full remission of their disease. The benefit-risk ratio of both conventional and high doses of prednisone in HB\textsubscript{s}Ag positive severe CALD needs further clarification.

The discovery of HB\textsubscript{s}Ag as a serum marker of hepatitis B virus (Blumberg et al., 1967) allows identification of patients in whom initiation and/or perpetuation of the liver disease is attributable to hepatitis B infection. However, the specific features of CALD associated with HB\textsubscript{s}Ag in CALD are poorly defined.

Several investigators (Bulkley et al., 1970; Dudley et al., 1972; Finlayson et al., 1972; Reed et al., 1973; Van Waes et al., 1974) have compared findings in groups of HB\textsubscript{s}Ag positive and negative CALD, which were not selected by pre-established criteria. Differences in sex, age, and incidence of non-organ specific immunoserological markers have been described, but only the predominance of males in HB\textsubscript{s}Ag positive CALD as opposed to the female predominance in HB\textsubscript{s}Ag negative cases has been a uniform finding. Chronic hepatitis associated with HB\textsubscript{s}Ag has been considered to have a milder course and better prognosis than when the antigen is absent (Sherlock, 1974). One retrospective report (Dudley et al., 1973) indicates that prednisone therapy in HB\textsubscript{s}Ag positive chronic liver disease is followed by clinical and biochemical improvement, but fails to define a definite therapeutic role of corticosteroids, whereas another (Aronoff et al., 1973) suggests that prednisone and/or azathioprine might have an adverse effect.

We have a treatment programme for patients with severe CALD who differ from those in other series by their homogeneity, particularly with regard to the severity of the liver disease, standardisation of therapies, and regularity of follow-up (Soloway et al., 1972). The presence or absence of HB\textsubscript{s}Ag were not factors in selection or subsequent treatment. A comparison of HB\textsubscript{s}Ag positive and negative patients in this group has been made to

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investigate differences in responses to therapy with prednisone, as well as to clarify variations in initial clinical and immunoserological features.

**Methods**

Postpubertal patients were eligible for our treatment programme if they fulfilled the predetermined criteria of chronicity and activity and had features compatible with CALD on liver biopsy. Chronicity was defined as disease duration of 10 weeks without improvement, or the presence of cirrhosis on liver biopsy. Activity was defined as SGOT elevation × 10 upper limit of normal (N 24 IU/l) or SGOT elevation × 5 in combination with a two-fold or more increase in gamma (N 1-6 g/dl) (Geall et al., 1968; Soloway et al., 1972). Histological features included chronic active ('aggressive') hepatitis (de Groote et al., 1968); subacute hepatitis, characterised by bridging or multilobular necrosis; or cirrhosis with active hepatitis (Baggenstos et al., 1972). Coded biopsies were interpreted by the same observer, who also recorded the presence and degree of features consistent with viral hepatitis (acidophilic cell necrosis, cell ballooning, lobular disarray, and Kupffer cell hyperplasia). Alcoholic liver disease, primary biliary cirrhosis, Wilson's disease, drug-induced liver disease, and other conditions were excluded by appropriate methods.

One hundred and thirty-six patients who were randomised to different therapies form the basis of the current report. Treatments (Soloway et al., 1972; Summerskill et al., 1975) comprised maintenance doses of prednisone (20 mg daily), prednisone (10 mg daily) together with azathioprine (50 mg daily) or prednisone given on alternate days in doses sufficient to suppress abnormal liver function tests (mean 20 mg on alternate days; range 10-50 mg). In all instances, higher doses of prednisone were given initially. In addition, some patients had been randomised to azathioprine (100 mg daily) or placebo until 1971, when these were discontinued because of inferior results (Soloway et al., 1972).

Patients were seen at six month intervals, when standardised clinical, biochemical, immunoserological, and histological evaluation was performed. Results of treatment comprised clinical and biochemical resolution; full (histological) remission; treatment failure and death (Soloway et al., 1972). Clinical and biochemical resolution comprised absence of symptoms, return of the patient to customary activities, and normal results of standard liver function tests, apart from a two-fold elevation of SGOT. Full remission, in addition to these features, required disappearance from the liver biopsy of histological features of disease activity, the appearances being normal or those of non-specific (identical with chronic persistent) hepatitis. Treatment failure was defined as the onset of hepatic coma, the development of ascites, increasing jaundice (serum bilirubin 66% above the lowest previous level and above 4 mg %) or a 66% increase in SGOT above the lowest previous value during treatment.

HBsAg was sought in initial and serial six month serum samples (stored at −10°C) by radioimmunoassay (Ausria II Abbott) (Ling and Overby, 1972); the passive hemagglutination test (Vyas and Shulman, 1970) and, later, a radioimmunoassay (Ausab, Abbott) (Peterson et al., 1973) were used for detection of anti-HBs. These measurements, as well as other biochemical and immunoserological determinations, were made in laboratories unaware of the diagnosis.

Eighteen patients had HBsAg detected in their serum on at least one occasion and six patients had anti-HBs; 112 patients were repeatedly negative for HBsAg and anti-HBs. All patients except one were North American Caucasians without a history of drug addiction. HBsAg positive patients were compared with HBsAg and anti-HBs negative patients for clinical, biochemical, immunoserological, and histological variables, and response to treatment. Statistical analyses were done by chi-square analysis or Fisher's exact test, for dichotomous variables, and by Wilcoxon rank sum tests for continuous variables. Because of possible interrelationships between the variables under study, linear discrimination methods were subsequently used to select that subset of variables which best contributed to discrimination between the HBsAg positive and negative patients. The variables employed were age, sex, SGOT, bilirubin, prothrombin time, serum albumin, serum gamma globulin, presence of associated immunopathic disease, and immunoserology.

Survival curves were calculated by the product limit method (Kaplan and Meier, 1958). Since major differences in sex, age, and immunoserology were found between the groups, the responses to treatment in the HBsAg positive group were also compared with that of HBsAg negative groups of similar size, matched for histology, treatment group, sex, age, and immunoserology. Matching was done by an independent observer and by computer. Statistical evaluation was done by the use of Cochran's test for matched pairs (Cochran, 1950).

**Results**

**ENTRY FEATURES: ALL PATIENTS (Table 1)**

HBsAg positive patients showed a predominance of
males, in contrast with the female preponderance in HBsAg negative patients, and the age of HBsAg positive patients was greater. HBsAg negative patients had a higher incidence of associated immunopathic disease, comprising eight examples of ulcerative colitis, seven patients with thyroïdosis, and the remainder with Sjogren's syndrome, scleroderma, cutaneous lupus erythematosus, rheumatoid arthritis, iritis, myasthenia gravis, idiopathic thrombocytopenic purpura, or pernicious anaemia. By contrast, diseases attributable to HB antigen-antibody complex deposition (Gocke et al., 1970; Combes et al., 1971) were limited to two HBsAg positive patients with periarteritis nodosa and immune-complex glomerulonephritis respectively.

Abnormalities in serum bilirubin, albumin, and gamma globulin were less in patients with HBsAg, but results of other liver function tests were similar. Differences were found in the incidence of so-called immunoserological markers. Lupus erythematosus (LE) cell, antinuclear antibody (ANA), smooth muscle antibody (SMA), and antimitochondrial antibody (AMA) were all negative in approximately 50% of HBsAg positive patients, whereas one or more tests were positive in high titre (≥ 1:40) in 75% of the HBsAg negative patients.

The extent and characteristics of the histological lesions in HBsAg positive CALD resembled those in the negative group. In particular, histological features consistent with viral hepatitis were equally frequent in both.

By linear discrimination methods, the subset of variables making a significant contribution were those representing immunoserology, age, and sex, in that order. The resulting discriminant function gave median values of 6.0 for the HBsAg negative and 0.8 for the HBsAg positive. The region of overlap between the groups (scores less than 4) contained all 18 HBsAg positive patients and only 17% of the 112 negative patients. The total ranges of the scores was −1.4 to +3.85 for positive patients and −0.4 to +8.1 for those who were negative. Thus, differences in sex, age, and immunoserology each remained significant.

Responses to treatment with prednisone (Table 2)

Of the 18 HBsAg positive patients, 13 treated with prednisone, with or without azathioprine, have reached an end-point (histological remission or treatment failure) or have been treated for longer than 12 months (average 24 months). HBsAg positive patients reached clinical and biochemical resolution and histological remission significantly less frequently when compared with all 82 patients without HBsAg who received prednisone treatment. Also, treatment failure and death were significantly more frequent in HBsAg positive patients.

When these 13 HBsAg positive patients were compared with the same number of matched HBsAg negative patients, HBsAg positive patients again reach histological remission less frequently and often become treatment failures.

Initial responses of patients to higher (60 mg daily) doses of prednisone or of the combination (prednisone 30 mg and azathioprine 50 mg daily) were usually as favourable as in HBsAg negative patients, although two HBsAg positive patients died during the first month of treatment. However, when doses were reduced to our conventional maintenance levels by a standardised procedure (Soloway et al., 1972), biochemical deterioration followed in six of 11 (54% surviving HBsAg positive patients) but occurred in only one of 13 (8%) of HBsAg negative patients (Fig. 1). Reinstatement of

Table 1 Initial features in chronic active liver disease (all patients)

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>HBsAg pos (18)</th>
<th>HBsAg neg (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>13 (89)</td>
<td>34 (30)*</td>
</tr>
<tr>
<td>Age, yr (median)</td>
<td>52</td>
<td>35*</td>
</tr>
<tr>
<td>Duration of symptoms &gt;12 mo</td>
<td>10 (56)</td>
<td>37 (33)</td>
</tr>
<tr>
<td>Ascites</td>
<td>2 (11)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Associated immunopathic diseases</td>
<td>1 (6)</td>
<td>31 (28)*</td>
</tr>
</tbody>
</table>

**Biochemical features**

<table>
<thead>
<tr>
<th></th>
<th>HBsAg pos (18)</th>
<th>HBsAg neg (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin, mg/dl (median) N: &lt;1:1</td>
<td>1-9</td>
<td>3-8*</td>
</tr>
<tr>
<td>SGOT IU/l (median) N ≤ 24</td>
<td>502</td>
<td>515</td>
</tr>
<tr>
<td>Prothrombin time, s (median) N ≤ 19</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Albumin, g/dl (median) N ≤ 3-3</td>
<td>3-4</td>
<td>2-8*</td>
</tr>
<tr>
<td>Gamma globulin, g/dl (median) N ≤ 1-6</td>
<td>2-2</td>
<td>3-3*</td>
</tr>
</tbody>
</table>

**Immunoserological features**

<table>
<thead>
<tr>
<th></th>
<th>HBsAg pos (18)</th>
<th>HBsAg neg (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE, ANA, SMA, or AMA, neg</td>
<td>10 (56)</td>
<td>7 (6)*</td>
</tr>
<tr>
<td>LE, ANA, or SMA ≥ 1:40 pos</td>
<td>1 (6)</td>
<td>85 (76)*</td>
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</tbody>
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**Histological features**

<table>
<thead>
<tr>
<th></th>
<th>HBsAg pos (18)</th>
<th>HBsAg neg (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic active hepatitis</td>
<td>4 (22)</td>
<td>29 (26)</td>
</tr>
<tr>
<td>Subacute hepatitis</td>
<td>9 (50)</td>
<td>59 (33)</td>
</tr>
<tr>
<td>Cirrhosis with active hepatitis</td>
<td>5 (28)</td>
<td>23 (21)</td>
</tr>
<tr>
<td>'Viral features' (in addition)</td>
<td>7 (39)</td>
<td>45 (40)</td>
</tr>
</tbody>
</table>

*P < 0.05. Percentages in parentheses.

Table 2 Response to prednisone therapy in HBsAg positive and HBsAg negative CALD†

<table>
<thead>
<tr>
<th></th>
<th>HBsAg pos (82)</th>
<th>HBsAg neg (13)</th>
<th>HBsAg neg† (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical and biochemical resolution</td>
<td>66 (80)*</td>
<td>6 (46)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Histological remission</td>
<td>56 (68)*</td>
<td>2 (15)</td>
<td>10 (77)*</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>13 (16)*</td>
<td>6 (46)</td>
<td>1 (8)*</td>
</tr>
<tr>
<td>Death, total</td>
<td>9 (11*)</td>
<td>4 (31)</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

*P < 0.05.
†Matched for morphology and treatment (type and duration), sex, age, and immunoserology. Percentages in parentheses.
higher doses of prednisone resulted in biochemical improvement in all.

Survival curves (Fig. 2) indicate that HBsAg positive patients treated with prednisone have a better prospect of survival than control patients, comprising three HBsAg positive and 26 negative patients who earlier received azathioprine or placebo. Direct comparison of HBsAg positive patients with or without prednisone was not feasible because of the small number of HBsAg positive patients on control therapy; however, the three HBsAg positive patients did not appear to have a more benign course (two deaths within three years) than HBsAg negative patients.

TREATMENT RESPONSE RELATED TO ANTIGENAEMIA

Ten HBsAg positive patients have been followed up for more than one year and the antigen has persisted in eight, seven of whom have required continuing treatment. In two patients antigaenaemia was transient. Both were under 40 years of age (whereas all but one of those with persistent antigaenaemia were older), and one reached full remission and discontinued treatment two years ago.

Discussion

The frequency of HBsAg in our patients with severe CALD was 14%. As prospective studies indicate that 50% of patients with HBsAg positive acute viral hepatitis who later develop chronic hepatitis eliminate all detectable amounts of antigen from their serum (Giles et al., 1969; Nielson et al., 1971; Redeker, 1972), our HBsAg and anti-HBs negative patients may include some whose disease was initiated by hepatitis B infection. If so, our HBsAg positive patients represent a subgroup characterised by failure to eliminate HBsAg early in their course.

In controlled circumstances, we found that HBsAg positive patients differ in several clinical and biochemical characteristics from HBsAg, anti-HBs negative patients. The predominance of males with HBsAg positive disease found in previous studies (Bulkley et al., 1970; Dudley et al., 1972; Reed et al., 1973) was confirmed. The higher age of patients with HBsAg positive disease has also been described in a patient population not addicted to drugs (Dudley et al., 1972) and our finding that patients eliminating the HBs antigen were younger may suggest that older individuals do this less effectively.

The association between CALD and ‘immunopathic’ diseases mainly involves HBsAg negative patients, whereas extrahepatic lesions attributable to HB antigen-antibody complexes typify those who are HBsAg positive. Similarly, the presence of non-organ specific immunoserological markers in high titres is greater in HBsAg negative patients, whereas their absence is commoner in those who were HBsAg positive. These findings support differences suggested by others (Bulkley et al., 1970; Finlayson et al., 1972; Dudley et al., 1973) but not universally confirmed (Reed et al., 1973; Van Waes et al., 1974). As the incidence of such ‘autoantibodies’ failed fully to differentiate between HBsAg positive and negative patients, and as weakly positive results were not infrequent in both groups, it appears likely that positivity of these
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tests represents alterations in host response, rather than specific aetiologies. Hence, the similar incidence of histological features associated with viral hepatitis in both groups is of interest.

Chronic hepatitis associated with HBsAg has been considered to have a better prognosis than when the antigen is absent (Sherlock, 1974). However, this generalisation cannot be substantiated when, as in our series, patients selected by uniform clinical, biochemical, and morphological criteria of disease severity are evaluated. In these conditions, we found that HBsAg positive patients with severe CALD enter remission significantly less frequently and fail therapy significantly more often than do negative patients when treated with prednisone, with or without azathioprine. This finding raises the question of the efficacy of treatment with steroids in HBsAg positive patients. While the benefit of steroids in CALD has been established in controlled trials Cook et al., 1971; (Soloway et al., 1972; Murray-Lyon et al., 1973), none of these has been restricted to HBsAg positive patients. Since the number of HBsAg positive patients in our control group was small, a valid comparison between prednisone treated and untreated patients with HBsAg was not possible. Our data, however, suggest that therapy is indicated and that higher doses of medication given over longer periods of time may be required for some patients with HBsAg, but the benefits and risks of such therapy await evaluation in a controlled trial.

We appreciate the continuing collaboration of our patients and their home physicians; gratefully acknowledge the assistance of Mrs Audrey Wolf, R.N., in the care of our patients; and are indebted to Dr A. H. Baggenstoss, who evaluated the liver biopsies, and to Dr P. J. Thomas for his continued advice in data analysis.

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Contrasting features and responses to treatment of severe chronic active liver disease with and without hepatitis BS antigen.

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