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Long-term follow-up of chronic active hepatitis of moderate severity

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SUMMARY A group of patients with only moderately active chronic hepatitis has been studied. The follow-up was long (mean 87 months). All patients except one were treated with prednisone and/or azathioprine. Of the hepatitis B virus positive patients two-thirds developed cirrhosis between the second and fifth year of evolution, while in the hepatitis B negative group this occurred in less than one-third. The transition to cirrhosis was clinically silent. The patients were all allowed to do their normal work except in the terminal stages of cirrhosis. Five patients died of causes related to the disease: three patients with cirrhosis and hepatocellular carcinoma, one with gallbladder carcinoma, and one from bleeding varices. The high incidence of tumour, especially liver-cell carcinoma, may be due to a cumulative effect of the presence of hepatitis B virus, cirrhotic transformation, and immunosuppression. The other patients are currently in apparently good health.

It is becoming increasingly evident that several agents may be involved in the pathogenesis of chronic hepatitis (Wright and Rassam, 1976). The observation and analysis of groups of patients with a high proportion of one of the known agents and similar onset is important for the evaluation of the clinical expression of the immunological trigger. Many groups of patients with chronic active hepatitis (CAH) have been studied from several viewpoints. They have been composed for the most part of hepatitis-B surface antigen (HBsAg) negative patients, especially in the Anglo-Saxon literature but less so on the European continent (Fox *et al.*, 1969; Wright *et al.*, 1969; Hadziyannis *et al.*, 1970; Mistilis *et al.*, 1970; Dubois *et al.*, 1972; Wewalka, 1972; Henning *et al.*, 1973). The present study analyses a group of patients with clinically almost inactive chronic hepatitis who have been followed-up for a very long period (up to 15 years) and almost all of whom have been treated with immunosuppressive drugs (prednisone and/or azathioprine).

Methods

PATIENTS

All 35 patients were observed at the Academisch Ziekenhuis K.U. Leuven, Belgium. They all lived in the country and were of Belgian origin. The patients were referred to this hospital in the years 1965-69 mostly as cases of unresolved acute hepatitis as shown by abnormal liver function tests. Some, however, were detected by chance during routine blood examination. They had very few clinical complaints. Because of this bias, most of our patients had a documented acute hepatitis before the onset of the chronic disease. They were taken into the study when the disturbances had lasted for at least six months.

In order to evaluate the state of the liver a needle biopsy was performed under laparoscopic control in all patients and repeated when necessary. The biopsies were analysed according to the criteria of De Groote *et al.* (1968). All the patients reviewed were classified as chronic aggressive hepatitis with moderate activity showing only slight piece meal necrosis and no overt bridging necrosis. According to the initial liver biopsy the group of patients was very homogeneous.

At the time of onset of the chronic disease in this group of patients the determination of the Australia antigen was not yet available. In the course of the disease and some years after the initial diagnosis it appeared that 17 patients were hepatitis-B virus positive (HBV) and 17 negative by radioimmunoassay for HBsAg. In one patient the determination has not been done.

No patient in the chronic state who had been HBsAg-positive later became negative. We are aware of only one patient (not included in this series) who had an HBV-positive acute hepatitis who lost the virus and nevertheless developed chronic disease. A biopsy taken more than six months after the acute stage in this patient showed the same

moderate activity as is described in this review. Subsequently it could be demonstrated that all other markers of HBV remained negative (surface, core and e antigen, and respective antibodies). This patient's disease stabilised at a low level and has not yet progressed to cirrhosis.

As in other series of HBV-positive chronic hepatitis the majority of patients were males (Table 1). No patients were clinically ill and they were allowed to do their normal work. The mean follow-up of the group was 87 months, ranging from 24 months to 186 months.

The classical liver tests were mostly maximal at the beginning of the chronic disease or at the first contact with the patient (Table 2). This seems partially due to the bias of referral. Nevertheless, 11 patients (31%) had higher levels of liver function tests during the follow-up than at the onset of chronicity. The liver tests and the inflammatory activity of the disease as observed in the needle biopsy regressed over the years also in those who developed cirrhosis. After five years 23 of the 25 patients and 19 out of 24 had normal or slightly raised transaminase levels and gamma globulin respectively. Markers of pathological immunity were not available at that time, but during the course of the disease, even during exacerbation, very few anti-tissue factors were observed and then only on one occasion (one LE, two AMF, one ANF).

COURSE OF DISEASE AND TREATMENT

All patients except one (HBsAg-negative, follow-up 38 months, stable CAH) were treated with immunosuppressive drugs, prednisone (10-15 mg daily) and azathioprine (50-100 mg daily). Only one patient received azathioprine (100 mg daily) alone because of diabetes. Therapy was started before knowledge of HBV status, and both positive and negative patients were treated. Before 1968 treatment was given more or less according to the variations of serum gamma globulins, whereas after 1968 patients were maintained on a fixed dose. Almost no side-effects were noted: only one patient had a reversible leucopenia of less than 60 000/mm^3, and two discontinued azathioprine because of gastrointestinal intolerance.

Two patients became pregnant, one during therapy and one twice after this was discontinued. Both patients were in the precirrhotic stage of the disease. All the pregnancies were uneventful and the children normal.

When treated patients were compared to their own situation two months before initiation of therapy the level of transaminases, gamma-globulin, and thymol turbidity was found to have fallen significantly ($P < 0.01$). When the HBsAg status of the patients later became available, no statistically significant difference was found between positive and negative groups for this initial effect of immunosuppression.

Table 1 *Characteristics of patients studied*

Sex	*HB virus*		*Age (years)*		
	+	−	*Median*	*Range*	
Male	12	9	46	32 −	64
Female	5	8	43	26 −	62
Total	17	17	—	—	

HBsAg was not determined in one male patient.

Table 2 *Level of SGPT and gamma globulin at start of chronic disease and during follow-up (HBsAG in serum + or −)*

		Start of chronic disease (years)									
		Onset		*2*		*3*		*4*		*>5*	
		+	−	+	−	+	−	+	−	+	−
SGPT	30	3	1	3	5	4	7	5	7	7	6
(IU/l)	100	4	4	8	5	8	6	9	5	6	4
	300	7	5	5	2	3	1	3	1	0	0
	500	3	5	1	0	2	1	0	0	2	0
Total		17	15	17	12	17	15	17	13	15	10
Gamma											
globulin	1, 5	9	5	13	5	7	8	8	6	7	6
(g/dl)	2	7	4	1	2	3	6	6	2	5	1
	3	1	2	0	0	1	2	2	2	2	0
	3	0	0	0	0	0	0	0	0	0	0
Total		17	11	14	7	11	16	16	10	14	7

Treatment was discontinued after at least one year's duration if SGPT remained consistently below 50 IU/l and liver biopsy showed either chronic persistent hepatitis or borderline chronic active hepatitis with or without cirrhotic transformation. An increase of SGPT above 150 IU/l and or gamma globulin above 2 g/dl was considered as a relapse (Table 3). By these criteria 13 patients relapsed: 11 (84%) soon (< six months) after stopping therapy and two respectively two and three years afterwards. In 12 patients therapy was resumed with apparent good effect on liver function tests. During the exacerbation there was no significant alteration of the clinical state. The majority of the relapses were observed in HB virus positive patients (70%) and in males (62%). The further follow-up of these patients one, two, four and more than five years after biopsy showed a trend towards improvement of the liver function tests both in patients who remained in the stage of chronic hepatitis and in those who developed cirrhosis (Table 2). After more than five years of follow-up all have SGPT values below 100 IU/l and gamma globulins below 2 g/dl except for

two HBV positive patients. Among the HBV negative patients 60% had completely normal transaminase and gamma globulin levels.

Results (Table 4)

After a mean follow-up of 87 months (range 40-186 months) 17 of the 35 patients (49%) passed into a stage of cirrhosis virtually without clinical symptoms. This happened more frequently in the HBV-positive patients: 12 or 71% against 5 or 31% in the HB virus negative patients. In contrast the HBV-negative patients reverted more often to chronic persistent hepatitis without cirrhosis: seven against one. One chronic ingester of oxyphenisatin also developed cirrhosis; she was HBV-negative. In one patient whose diagnosis remained CAH, the HBV in serum was not determined.

Table 3 *Relapses (SGPT > 150 IU/l and/or gamma globulins > 2 g/dl analysed according to sex and HBV status*

Sex	*HBV*	*Relapse*	
		+	−
Male	+	7	6
	−	1	7
Female	+	2	3
	−	3	3
Total		13	19

Table 4 *Outcome of disease related to sex and HBV status (mean follow-up of 87 months)*

Sex	*HBV*	*CPH*	*CAH*	*Cirrhosis*	*Total followed*	
Male	+	0	3	9	12	
						17
Female	+	1	1	3	5	
Male	−	4	3	2	9	
						16
Female	−	3	1	3	7	
Total		8	8	17		33

CPH: Chronic persistent hepatitis. CAH: Chronic active hepatitis (moderate).
Not included: (1) Patient (male) HBV?: CAH. (2) Patient (female) HBV: CAH + bile duct sclerosis.

In all but one of the patients who developed cirrhosis, this happened between the second and the fifth year of the disease. Only one patient was already cirrhotic one year after the onset of the disease. No clinical differences were noted during the first two years of the disease between those who later developed cirrhosis and those who did not. Only a higher frequency of raised SGPT (> 100 IU/1) occurring at least once a year during the first two years of chronicity seemed of prognostic value. Among these patients 13 out of 17 (76%) eventually developed cirrhosis as against 49% of the total group. However, of these 17 patients 12 (71%) were also HBV-positive. A rise of gamma globulin over 2 g/dl in the first two years was not accompanied by a higher incidence of cirrhosis. Two patients are HBV-negative but have repeatedly shown high levels of anticore antibody; these are still in the same stage of chronic active hepatitis after 86 and 117 months respectively.

In our material the prognosis of chronic active hepatitis of moderate severity due to HBV was worse than that of the HBV-negative forms. Indeed, not only did more patients develop cirrhosis (71% compared to 29% respectively) but also more patients died from a complication of the disease during the follow-up period: three from cirrhosis with hepatocellular carcinoma, one from a gallbladder carcinoma, and one from bleeding varices. One HB virus negative patient died from a bleeding peptic ulcer. The figure of four patients (33%) with malignant disease among the cirrhotic patients associated with HBV seems to be very high. There have been many reports confirming a relationship of the hepatitis B virus and hepatocellular carcinoma. The published reports are more concerned with patients in the younger age groups and with very rapidly developing small nodular carcinomas (Alpert *et al.*, 1969). Our three patients were middle-aged, with slower evolution of the malignancy and with larger and fewer nodules. These tumours developed 74, 95, and 108 months after onset of the chronic disease. It is also noteworthy that all these patients were treated with immunosuppressive drugs. Although mostly lymphoid tumours are described after this form of therapy, long-standing immunosuppression in HBV positive patients may be dangerous, in that the cirrhotic transformation, the virus, and the therapy may have a cumulative carcinogenic action.

Discussion

The evolution and outcome in this group of patients with moderately active chronic hepatitis, with a majority of HBV positive patients, seem to be very different from the more active form of the disease. The great majority of the patients are male, middle-aged, symptomless, and at their normal work. In most instances the disease started with an attack of acute hepatitis clinically similar to that in patients with a normal evolution. Although it has been shown that the hepatitis-B virus usually persists in the chronic stage, one patient was observed in 1970 who was positive during the acute state and whose disease became chronic, although she apparently lost the HBs antigen. In an analogous series from the

same hospital Ray *et al.* (1976a, b) were able to demonstrate with immunofluorescent techniques that 10% of patients who were HBV seronegative had positive specific fluorescence for HBsAg on biopsy. The antigen was localised in liver-cell membranes as well as in the cytoplasm.

The evolution into cirrhosis is rather slow and occurred between the second and the fifth year of the chronic disease. As immunosuppressive therapy was given to all but one patient, it is not possible to judge the effect of therapy on the mode and time of onset of the cirrhotic transformation and on the general evolution of these patients. A controlled study of long duration is needed in order to appreciate the influence of therapy. Indeed, on the one hand half of the patients developed cirrhosis practically without symptoms notwithstanding classical immunosuppressive therapy of long duration, while on the other hand the appearance of three hepatocellular carcinomas and one gallbladder carcinoma seems a very high incidence in this small series.

As in the more active forms of CAH, the HBsAg positive patients did worse than the negative ones, although on the whole their course was more favourable than that of more active HBV negative CAH. Only four patients died of liver complications after a follow-up period of 100 months. Exacerbations with increase of transaminases above 100 IU/l or gamma globulin above 2 g/dl were seen in only two (HBV positive) patients out of 35 (6%) after the fifth year of the disease.

The present series shows clearly that patients with a clinical picture of unresolved acute hepatitis may develop serious liver disease. Liver biopsy is necessary for full assessment, and absence of serious clinical symptoms and severe biochemical disturbances does not necessarily indicate mild, non-progressive liver disease. Cirrhosis may develop over a period of years and remain clinically silent. Eventually these patients developed all complications of the cirrhotic stage.

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