Prognostic value of HBeAg in chronic persistent hepatitis

Although chronic persistent hepatitis is generally a benign, self-limiting condition with a good prognosis,¹ some cases progress to chronic aggressive hepatitis.^{2,3} There are no criteria for predicting whether the disease will progress to the aggressive form. The e antigen (HBeAg) may provide a new method for appraising the prognosis in HBsAg hepatitis, both acute and chronic,^{4,5} and we undertook this study to define the relation between the behaviour of the HBeAg/anti-HBe system and the prognosis in patients with chronic progressive hepatitis.

Patients, methods, and results

Thirty-five consecutive patients with HBsAg/anti-HBs-positive chronic progressive hepatitis were followed up by serial biochemical and biopsy tests for one to five years. The diagnosis was confirmed histologically by two pathologists. Twenty-five of the 35 patients examined had a history of overt hepatitis; 21 of them were HBsAg-positive and four had anti-HBs. These patients had a liver biopsy six to 12 months after the acute episode. The remaining 10 patients had no history of hepatitis, although four were HBsAg-positive and six anti-HBs-positive. None of these patients received steroids or immunosuppressive treatment during the observation period. We carried out the HBeAg/anti-HBe tests by a standard immunodiffusion technique,⁴ using laboratory reagents that had been tested for identity with standard sera kindly provided by Dr P Holland (National Institutes of Health, Bethesda). HBsAg and anti-HBs were detected by radioimmunoassay with Ausria II and Ausab (Abbott Laboratories). Twelve of the 35 patients showed biochemical and histological resolution of liver disease over 12 months (see table). Four of them carried anti-HBe and two HBeAg. These two patients lost HBeAg after six and seven months respectively. Fifteen showed no biochemical or histological changes during a mean of 24 months' observation. Of these patients, five were carriers of anti-HBe and six of HBeAg. Only two of these HBeAg-positive patients lost their initial HBeAg positivity despite persistence of HBsAg. Finally, eight patients developed chronic aggressive hepatitis (six cases) or cirrhosis (two) within six months to three years. All these eight patients had HBeAg in their serum and only one showed seroconversion of HBeAg positivity during observation. In this patient seroconversion occurred when histological examination showed inactive cirrhosis.

Comment

The clinical and therapeutic relevance of these findings is supported by a striking difference ($P<0.025$) in the incidence of HBeAg and anti-HBe between those patients who recovered or had no progression of their illness and those who developed a more severe form of the disease. HBeAg was commoner in patients with overt acute hepatitis (56%) than in those without (20%). In this second group recovery was commoner and no patient developed more active liver disease. Our data suggest that loss of HBeAg in chronic progressive hepatitis may be an important prognostic sign indicating resolution of the illness; it occurred in both patients who recovered completely. Persistence of HBeAg, on the other hand, may be associated with an impaired immune response to the hepatitis B virus. Patients with chronic progressive hepatitis and HBeAg in their serum thus seem likely to have a poor prognosis and to need particularly

careful follow-up so that corticosteroids may be given at the first sign of chronic aggressive hepatitis, whereas patients who are HBeAg-negative or briefly HBeAg-positive or have anti-HBe need no treatment.

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1 Becker, M D, *et al*, *Lancet*, 1970, **1**, 53.
2 Vido, I, *et al*, *Deutsche medizinische Wochenschrift*, 1969, **94**, 221.
3 Smith, M G M, Eddleston, A L W F, and Williams, R, *Clinics in Gastroenterology*, 1975, **4**, 311.
4 Magnus, L O, and Espmark, J A, *Journal of Immunology*, 1972, **109**, 1017.
5 Nielson, J O, Dietrichson, O, and Juhl, E, *Lancet*, 1974, **2**, 913.

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Sleep deprivation in patients undergoing operation: a factor in the stress of surgery

Patients expect to have sleep disturbance when admitted to hospital and often joke about it. Their view is supported by the frequent prescription of hypnotics by doctors and nurses to ease an apparent burden of sleeplessness. We carried out the present study to establish the degree of sleep deprivation and disturbance in surgical patients; the alteration in their sleep profile; and the amount of disturbance caused by pain, noise, and other environmental factors.

Patients, methods, and results

Patients who were to undergo elective surgical procedures answered a questionnaire on admission about their sleeping habits at home and completed an Eysenck personality inventory. Each subsequent morning while in hospital they were interviewed and completed a questionnaire about their previous night's sleep. Operations were arbitrarily divided into mild (for example, endoscopy and herniorrhaphy) and severe (for example, cholecystectomy and multivisceral resections). One hundred and ten consecutive patients admitted to the academic surgical unit between March and September 1976 entered the study but 17 were excluded because of persistent refusal or inability to complete the questionnaire (10); admission to the intensive care unit for more than 48 hours (2); and abnormal—that is, five or more—neurotic or "lie" scores on the Eysenck personality inventory.

Incidence of HBeAg and anti-HBe in patients with HBsAg/anti-HBs-positive CPH in relation to clinical course and prognosis

	Recovered		Unchanged		Progressed to CAH or cirrhosis	
	HBeAg +	Anti-HBe +	HBeAg +	Anti-HBe +	HBeAg +	Anti-HBe +
Patients with history of overt acute hepatitis (n = 25)						
HBsAg + (n = 21)	2	2	3	4	7	
Anti-HBs + (n = 4)		1	1		1	
Seroconverted HBeAg + to HBeAg -	2		1		1	
Continued HBeAg +			3			
Total in group	6		11		8	
Patients with no history of previous acute hepatitis (n = 10)						
HBsAg + (n = 4)			2			
Anti-HBs + (n = 6)		1		1		
Seroconverted HBeAg + to HBeAg -			1			
Continued HBeAg +			1			
Total in group	6		4			
All patients (n = 35)	12 (34.3%)	4 (33.3%)	15 (42.9%)	5 (33.3%)	8 (22.9%)	
	2 (16.7%)		6 (40.0%)		8 (100.0%)	

Routine hypnotics and pain relief were prescribed by ward staff not associated with the study.

Though five patients claimed to be bad sleepers at home and four more regularly took hypnotics, the striking finding was a reduction of the mean duration of sleep both before and after surgery over the ten days of the study (see figure). More detailed analysis of the sleep patterns showed that the deficit was principally due to early awakening, though there was also more delay in getting to sleep. Patients also recorded a decrease in the quality of the sleep, increased awakenings, and, in the first three postoperative days, much disturbance by both noise and pain. Only two-thirds of the severe group and one-third of the mild group received intramuscular analgesia on the first postoperative night.

Discussion

We have provided evidence to support anecdotes that acute hospitals with open wards are not places in which it is easy to obtain a sound night's sleep. Two other points are suggested by the results of this study: firstly, that pain relief receives less attention than it should; and secondly, that the further decrease in sleep after injury may, because it is long lasting, represent a primary effect of surgery and anaesthesia on the brain.

Copies of the sleep questionnaire and the detailed data are available from HD.

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Failure of heparin to alter the outcome of pneumococcal meningitis

Pneumococcal meningitis continues to carry a high death rate, especially in tropical Africa.¹ The reason for this is not clear.² Post-mortem studies³ and the presence of raised concentrations of fibrin degradation products (FDP) in the cerebrospinal fluid (CSF) of patients suggest that cerebral vascular thrombosis may be important. We therefore tried treating pneumococcal meningitis with heparin.

Patients and treatment

From November 1976 to March 1977 15 adults with proved pneumococcal meningitis were admitted to this hospital. They were allocated randomly to control or heparin-treatment groups. All patients received intravenous penicillin in a dose of 24 megaunits/24 hours for five days, followed by a smaller intramuscular dose for a further five days. Patients treated with heparin received an initial intravenous dose of 10 000 units followed by 30 000 units/24 hours for five days given by continuous intravenous infusion. Clotting times, checked regularly, were always less than twice the control.

Detailed clinical observations were made daily on all patients. Blood and CSF were collected on admission, one, two, three, and five days later and, in the survivors, 24 hours after ending penicillin treatment. All CSF samples were examined by Gram stain and cultured on blood agar. CSF leucocyte and bacterial count, protein content, and lactate concentration were measured by standard techniques, and serum and CSF were tested for pneumococcal antigen by counter-current immunoelectrophoresis.⁴ Platelet counts, FDP concentrations, and kaolin cephalin clotting times were measured by standard methods.

The presenting clinical features in the two groups were similar (table). Four patients treated with heparin died but among the controls only two deaths occurred. Persistent blood staining of CSF was observed in the daily samples of three of the patients treated with heparin but in none of the controls.

Two patients in the control group showed laboratory, but no clinical, features of mild disseminated intravascular coagulation and one of these patients died. Gram-positive cocci were seen in the CSF of four of five surviving heparin-treated patients three days after the start of treatment and in two of six surviving controls. The results of all cultures were negative at this time. Cerebrospinal fluid cell and bacterial counts, protein, lactate, and FDP concentrations were all high on presentation and fell progressively during treatment but no significant differences were found between the heparin-treated and control patients.

Comment

Intravenous heparin in the dose that we used is of no value in treating pneumococcal meningitis. Four of the six patients who died were treated with heparin and new focal neurological signs developed in four heparin-treated patients but in only two controls.

The persistent blood staining of the CSF in three patients treated with heparin suggests that heparin may be dangerous in this condition. Owing to local beliefs a necropsy could not be performed to see if heparin had contributed to the death of patients in this treatment group. In one patient, however, bilateral burr holes were made after the development of a hemiplegia, but no cerebral bleeding was found.

Disseminated intravascular coagulation is a recognised but rare complication of severe pneumococcal infection.⁵ It is unlikely, however, that mild disseminated intravascular coagulation of the type seen in two of our patients, or its prevention by heparin, could be important in determining the outcome of the infection.

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- ¹ Baird, D R, Whittle, H C, and Greenwood, B M, *Lancet*, 1976, **2**, 1344.
- ² Tugwell, P, Greenwood, B M, and Warrell, D A, *Quarterly Journal of Medicine*, 1976, **180**, 583.
- ³ Dickson, L G, and Yassin, M W, *Journal of the Egyptian Public Health Association*, 1969, **44**, 349.
- ⁴ Greenwood, B M, and Whittle, H C, *Clinical and Experimental Immunology*, 1974, **16**, 413.
- ⁵ Rytel, M W, et al, *The American Journal of Medicine*, 1974, **57**, 889.

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Clinical features and clinical course of patients with pneumococcal meningitis treated with heparin and of control patients

	No of cases	Mean age in years (range)	Patients with coma on admission	Patients with focal neurological signs on admission	Deaths	Days to full consciousness in survivors (SD)	Patients with new focal neurological signs developing during treatment
Heparin group	7	24 (13-40)	4	4	4	6.3 ± 5.0	4
Control group	8	28 (12-50)	3	2	2	6.0 ± 2.5	2