Papers and Originals

Hepatitis-associated Antigen and Antibody in Haemodialysis Patients and Staff

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Summary: The screening of a dialysis population for the presence of hepatitis-associated antigen (H.A. antigen) has proved to be of value in locating a probable source of infection and in terminating an outbreak of hepatitis by early detection of H.A. antigen positive patients and staff.

Introduction

Epidemic hepatitis is a well-recognized hazard to patients and staff of maintenance haemodialysis units (Jones *et al.*, 1967; Drukker *et al.*, 1968). The renal unit of the Royal Free Hospital has not escaped, cases of hepatitis having been diagnosed on three occasions. In October 1965 a single case closely related to blood transfusion occurred, while in May 1968 two patients developed hepatitis. The attack proved to be fatal in one patient, her husband also dying of hepatitis eight weeks later. In 1965 and 1968 after isolation of the infected patients no further cases occurred either in patients or in staff as judged clinically and by regular screening for serum aspartate transaminase (AsT). Between April and October 1969 11 cases of hepatitis occurred, involving three patients and eight members of the staff. In May 1969 after the beginning of this larger outbreak it was possible to screen the dialysis population by detection of H.A. antigen.

This antigen has been found in the blood of patients late in the incubation period and early in the acute phase of serum hepatitis (Prince, 1968a). It is suggested that a positive test for the antigen is related to the presence of hepatitis virus. A further study on the patients involved in the outbreak described by Jones *et al.* (1967) showed by using Prince's antiserum that the antigen had persisted in 9 out of 17 patients on maintenance haemodialysis. Six of these had histories of hepatitis. In one patient the test was still positive after three years (Turner and Bruce White, 1969). Clinical and laboratory features of hepatitis in the staff and the patients on dialysis have been noted to be different. The staff have a typical acute hepatitis with much higher levels of AsT and transient antigenaemia; whereas patients either are completely symptomless or manifest a chronic anicteric state, with minimally raised AsT levels but prolonged antigenaemia (London *et al.*, 1969). The results of screening the dialysis population of the Royal Free Hospital during 1969 are here reported.

Material and Methods

Dialysis Unit, Patients, and Staff.—The present unit, in use from September 1968, has 13 haemodialysis stations. One hundred patients have been treated—80 having home dialysis, 12 permanently based on the unit, and 8 are in training for home dialysis. Approximately 80 to 110 haemodialyses are carried out in the unit each week. Only half of these dialyses are routine: the remainder involve patients who are in training, who have been readmitted for medical reasons, or who have recently received a renal transplant. Approximately 15 patients a week also attend for transplantation follow-up, home dialysis medical check-ups, or emergencies. The total number of staff, including the changing population of medical, technical, and lay members allocated to the unit, approaches 50.

Dialysis Technique (Baillod *et al.*, 1968).—Each patient receives at least 30 hours of haemodialysis a week—usually in three 10-hour periods, or more frequent shorter periods in the case of patients who are ill. Dialysis is by single passage through Kiil dialysers sterilized by formalin, heat-sterilized single-patient automatic dialysate supply and control units being used. Each patient has his own dialyser, which is re-used up to three times. Use is made of sterile disposable packs, lines, syringes, and needles, and each patient is allocated his own non-disposable items. Access to the blood stream is by means of an external arteriovenous shunt (Quinton *et al.*, 1962) or an internal arteriovenous fistula (Brescia *et al.*, 1966)—requiring repeated venepuncture. Blood transfusion is rarely used, but when necessary it is given to replace acute blood loss (Crockett *et al.*, 1968).

H.A. Antigen and Antibody Screening.—From May 1969 the staff and patients have been screened at two- to four-week intervals. Patients dialysing at home were screened at longer intervals. In all 94 patients and 82 staff were screened. Serum was stored at -20°C. or plated within 24 hours, using the two-dimensional immunodiffusion technique previously described (Fox *et al.*). Antisera used for the detection of H.A. antigen were obtained from a multiple transfused haemophiliac and an antibody-positive nursing sister. This sister had worked on the dialysis unit for 18 months, had never received a blood transfusion or had clinical hepatitis, and was perfectly well, liver function tests being normal. Both antisera showed identical specificity to the reference antisera of Blumberg *et al.* (1965) and Prince (1968b).

AsT Estimations.—These estimations (Morgenstern *et al.*, 1966) were carried out with the same frequency as those for H.A. antigen.

Use of Gammaglobulin.—Previous to the 1969 outbreak staff and patients dialysing in hospital received gammaglobulin at approximately six-monthly intervals. Since May 1969 gammaglobulin (750 mg. intramuscularly) has been offered every six weeks. Not all members of staff wished to avail themselves of this.

Results

Staff

Eight members of staff suffered attacks of hepatitis and a further two were found to be positive for H.A. antigen,

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TABLE I.—*Staff Affected by Hepatitis or Positive H.A. Antigen*

Case No.	Category	Hepatitis History	γ-globulin Given Within 6 Weeks of Hepatitis	Maximum Aspartate Transaminase (i.u./litre) (Normal Range 5-17 i.u./litre)	Antigenaemia	
					Acute	Prolonged
S1	N	Icteric	—	92 (AIT)	—	—
S2	D	Icteric	—	1,900	—	—
S3	D	Anicteric	—	300	—	—
S4	N	Icteric	+	1,000	—	—
S5	N	Icteric	+	720	+	
S6	N	Asymptomatic	+	10		+
S7	D	Icteric	—	450	+	
S8	N	Icteric	+	970	+	
S9	L	Icteric	—	750	+	
S10	L	Asymptomatic	—	10		+

Category: N = Nurse; D = Doctor; L = Laboratory technician.

though they remained symptom-free (Table I). Seven had icteric attacks, four of these being severe (one with precoma). The remaining case was anicteric, with a maximum AsT of 300 i.u./litre. No deaths occurred. Persistence of raised AsT varied from 3 to 12 weeks, but recovery was eventually complete in all cases. There was no difference in the severity or length of attack between the group who received gammaglobulin within the six weeks before the development of hepatitis (three cases) and the group who did not (five cases).

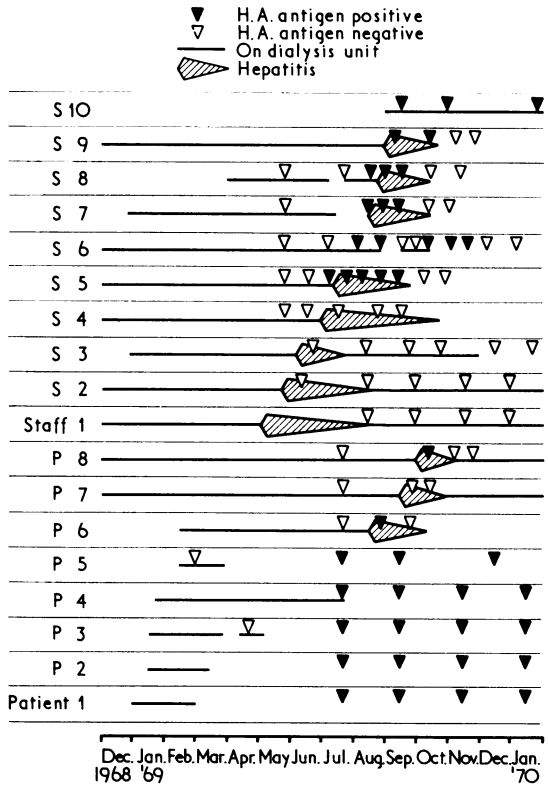
The H.A. antigen was negative in four of the eight members of staff who had attacks of hepatitis, though in three of these the blood was not tested during the first week of the clinical illness. In the four H.A. antigen positive cases who had clinical hepatitis the antigenaemia was acute, with a range of one to five weeks. In two cases the antigenaemia was detected a few days before the clinical symptoms. The two asymptomatic members of staff with positive H.A. antigen had prolonged antigenaemia. One was Rhod[illegible]n and one Nigerian. Five to eight per cent. of tropical [illegible]pulations are H.A. antigen positive (Blumberg *et al.*, 1968).

Despite screening, no case of hepatitis or positive H.A. antigen was detected in the relatives of H.A. antigen positive patients dialysing at home.

Patients

Though full screening of the staff was carried out in May, full screening of all patients for H.A. antigen was not carried out until July because of the numbers involved and the fact that many of the patients were at home. At this time five patients were found to have a positive H.A. antigen. None of these (Cases P1-5) had any clinical features to suggest hepatitis, though a modest rise of AsT was found in all but one (Table II). Gammaglobulin had not been given to any of these patients. In all five the antigenaemia was prolonged and has persisted over six months.

Of the patients with persistent antigenaemia one subsequently died of pulmonary tuberculosis and systemic candidiasis. Necropsy revealed no histological evidence of acute



or chronic hepatitis. Frozen sections of the liver were exposed to fluorescin conjugated antibody to H.A. antigen, and specific fluorescence of patchy distribution was seen throughout the section. The fluorescence was within the cytoplasm of the hepatocytes surrounding the nuclei.

Subsequent to the initial screening three other patients developed clinical attacks of hepatitis. Two cases were icteric, with a rise of AsT for three and four weeks. The third case was anicteric, the AsT level rose to the upper limit of normal only, and the symptoms lasted 10 days. No deaths occurred and rapid clinical recovery resulted in all three. Two of these three patients had received gammaglobulin within the six weeks before they developed hepatitis. Two of the three cases had acute antigenaemia lasting not more than seven days. The remaining case never became positive for H.A. antigen, though blood was examined within three days of the onset of symptoms.

Epidemiology (see Chart)

No member of the staff had any previous history of hepatitis or any known contact with the disease outside the unit. Case P1 had jaundice of unspecified aetiology associated

TABLE II.—*Patients Affected by Hepatitis or Positive H.A. Antigen*

Case No.	Haemodialysis Started	Home Dialysis Established	Hepatitis History	γ-globulin Given Within Six Weeks of Hepatitis	Date of Last Blood Transfusion	Maximum Aspartate Transaminase (i.u./litre) (Normal Range 5-17 i.u./litre)	Antigenaemia	
							Acute	Prolonged
			Symptom-free					
P1	30/12/68	3/3/69	Jaundice with acute renal failure (1957)	–	Dec. 1968	33		+
P2	9/1/69	13/3/69	?Anicteric hepatitis (May 1969)		Nil	85		+
P3	14/1/69	28/3/69	Nil	–	Feb. 1968	33		+
P4	20/1/69	28/7/69	Known hepatitis contact (April-June 1968)	–	Nov. 1968	13		+
P5	13/2/68	24/4/68	Nil		Feb. 1968	45		+
			Hepatitis					
P6	11/2/69	24/9/69	Icteric	–	Feb. 1969	270	+	
P7	1/10/64	Not intended	Icteric	+	Feb. 1964	500	–	
P8	13/1/64	Not intended	Anicteric	+	Feb. 1964	18	+	

with gastroenteritis and acute renal failure 12 years before haemodialysis was started. In the intervening period renal function had been adequate. Case P4 had developed renal failure with a right renal carbuncle and pyelonephritis due to septicaemia from self-administration of methadone. Two syringe contacts had hepatitis in April and June 1968 (retrospective discovery). Personality and psychological difficulties greatly complicated treatment in this man. Routine dialysis, with access to the blood stream by internal arteriovenous fistula, was frequently disrupted, resulting in blood spillage and staff intervention, with contamination. He eventually accepted his illness and subsequently co-operated. Nevertheless, when in July the positive antigenaemic state of Cases P1-5 became known, he was the only one of the five still dialysing in the hospital unit. He was immediately trained in self-venepuncture, and home dialysis was established within nine days by temporary installation.

The first clinical case in this outbreak occurred in a member of the staff 12 weeks after Case P4 began haemodialysis. The last occurred 10 weeks after he had been established on home dialysis. Of five patients revealed by initial screening to be H.A. antigen positive, Case P4 was the only one using a fistula for access to the blood stream. No other patient had had known contact with hepatitis outside the unit. Cases P3 and P5 were negative for H.A. antigen in March and February 1969 respectively (examination of stored frozen serum which does not lose antigenic properties over this period of time) (Turner and White 1969). The two patients surviving from earlier outbreaks in 1965 and 1968 were both negative for H.A. antigen.

Discussion

Source of Infection

It seems probable that Case P4 introduced the virus into the unit, since he was the only patient known to have had contact with other cases of hepatitis, the contact being via shared syringes and needles. The time relationship to his presence in the unit and the period of the outbreak is evident. Furthermore, he was the only one of the first five antigenaemic patients with a fistula for access to the blood stream. In our experience an external arteriovenous shunt has advantages for self dialysis in that there need be no blood spillage, whereas with a fistula some skin contamination with blood is inevitable. This contamination becomes a danger whenever it is necessary for doctors or nurses to introduce or adjust needles, as, for example, during the early stage of training. The fact that the training of Case P4 required frequent staff intervention increased the danger of contamination, and it is likely that the initial transfer of infection to the staff occurred at this stage.

The other four initially H.A. antigen positive patients, Cases P1, P2, P3, and P5, are unlikely to have started the outbreak. All four used an external shunt for access to the blood stream, thus carrying less danger of passage of infection. Case P1 had jaundice in 1957 and cannot be completely ruled out as the originator of this outbreak, since dialysis patients have been known to carry the H.A. antigen for at least three years (Turner and White, 1969). Nevertheless, it is not known whether or not this patient's earlier attack of jaundice was of viral aetiology.

Case P2 had an AsT of 85 i.u./litre (falling to 30 i.u./litre 10 weeks later) at the time that the screening was carried out in July, and therefore possibly sustained a subclinical attack of hepatitis then. Cases P3 and P5 may be confidently excluded, since their stored frozen sera was H.A. antigen negative in March and February respectively. It should be noted that, in accordance with the policy of minimal blood transfusion (Crockett, *et al.*, 1968), none of the eight patients had been given blood within six months of finding a positive H.A. antigen, making donor blood an unlikely vehicle of infection in this outbreak.

Route of Infection

In the environment of haemodialysis it is likely that an epidemic of hepatitis would be blood-borne. This is supported by the fact that the members of staff affected were all involved in direct contact with the patients or with blood samples, whereas no cases occurred among the ancillary staff. Minor skin abrasions are easily overlooked or forgotten, and no specific incident was reported. Formalin dermatitis, however, was present in Cases S1 and S5 and could have provided a portal of entry.

All five patients initially found to be H.A. antigen positive had ample opportunity for contact with each other and with the staff. The period of concurrent hospital dialysis varied between 4 and 14 weeks, and for at least part of this time these patients would have shared the same dialysis room. These factors do not apply to transfer of infection to Cases P6, P7, and P8. It will be seen, however, that these cases occurred shortly after the peak of the epidemic, when infectivity among the staff was at its highest. An additional factor in Case P7 is that he had a fistula for access to the blood stream, and until he developed hepatitis venepuncture was carried out by nursing or medical staff.

Value of H.A. Antigen Screening

By H.A. antigen screening the probable origin of the outbreak was discovered. The early detection of H.A. antigen positive cases allowed adequate isolation and precautions to be taken against further spread of infection. Thus screening revealed five symptomless patients who were H.A. antigen positive, two symptomless carriers among the staff were discovered, and two members of the staff were sent off duty before the onset of overt clinical symptoms. Finally, regular screening of the dialysis population, and especially of new patients and staff, has so far prevented the introduction of a fresh infection. It should be noted, however, that in two cases of hepatitis (one patient and one staff) the H.A. antigen was negative even though blood was examined during the acute stage (within three and seven days of the onset of symptoms respectively).

Clinical Course in Patients and Staff

Our experience partly supports the previous report of London *et al.* (1969), who distinguished between the clinical course of patients and staff. Thus 8 out of 10 members of staff had clinically manifest attacks of hepatitis with significantly raised AsT levels and antigenaemia which, when present, was not prolonged. Five symptomless patients were found with a minimal rise of AsT levels but prolonged antigenaemia. We find, however, that this distinction is not absolute. Thus two symptomless members of staff were found to have prolonged antigenaemia, and three dialysis patients had overt attacks of hepatitis with a rise of AsT to levels within the range found in the staff members who had clinical hepatitis. None of these three latter patients had prolonged antigenaemia.

It is of interest that the three patients who had hepatitis and became subsequently H.A. antigen negative were fit. On the other hand, the five symptomless patients with prolonged antigenaemia had either dialysed for a shorter length of time (their physical rehabilitation being thus incomplete) or they had been readmitted for reasons of medical illness (Cases P3 and P5). It is possible, therefore, that the two patterns of disease previously noted in staff and patients depend not on category but on the state of health of the subject when exposed to the virus. It appears that a person who is unfit at

the time of contact with the virus may, for reasons as yet unexplained, be incapable of mounting the host/virus response (clinical hepatitis), thus retaining the antigen. It is our experience that when a state of physical health is achieved subsequently by adequate haemodialysis the carrier state nevertheless persists.

It has been hoped that the state of physical health achieved through successful renal transplantation would terminate a prolonged carrier state. Two patients with prolonged antigenaemia, however, have remained carriers of H.A. antigen six and eight months after renal transplantation (J. S. Cameron, personal communication, 1970). The period of stay in hospital for transplantation will put the dialysis population at further risk. Furthermore, transplantation itself may introduce fresh hepatitis by increasing the number of immunosuppressed (and thus infection-prone) patients attached to the unit (Moore and Hume 1969) as well as the possibility of the virus in donor serum contaminating the kidney.

Conclusion

It is hoped that regular screening for H.A. antigen will avoid the introduction of positive cases into dialysis units and reduce the risk of epidemics. The precautions adopted at this centre include screening of prospective patients and staff as well as donated blood whenever possible. With regard to hygiene, the guidance of the Public Health Laboratory Service Report (1968) has been followed in order to avoid contact with blood and to isolate new cases of hepatitis requiring hospital dialysis. More important, however, is the continued emphasis on home dialysis. Though in this outbreak no relatives of patients with positive H.A. antigen dialysing at home developed hepatitis, they are undoubtedly at risk. Nevertheless, the further development of a self-dialysis technique to include self-venepuncture by patients using a fistula, both at home and in the unit, is a major safeguard.

The use of H.A. antigen has enabled the probable source of this outbreak to be located. In the early detection of fresh cases and in diagnosing the carrier state it has proved invaluable, and has undoubtedly contributed to an earlier termination of an epidemic which in a dialysis population of this size could have reached very much greater proportions.

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Glucose and Insulin Secretory Response Patterns Following Diet and Tolazamide Therapy in Diabetes

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Summary: Glucose and insulin secretory response patterns during glucose tolerance tests were determined in 28 maturity-onset diabetics, and the sequential effects of diet and a sulphonylurea, tolazamide, were assessed. Untreated diabetics showed hyperglycaemia, increased serum immunoreactive insulin response patterns, delayed insulin release, and relative insulin deficiency. Diet alone partially corrected the hyperglycaemia and serum immunoreactive insulin response but had no effect on the delayed insulin release or relative insulin deficiency. Tolazamide plus diet restored all values towards normal. The net effect of maintenance tolazamide therapy was to (1) restore the insulin secretory response pattern to normal, (2) reduce total pancreatic insulin output, and (3) improve the efficiency of insulin secretion. The results suggest that there is a rational basis for the use of sulphonylurea in all maturity-onset diabetics, including patients with mild carbohydrate intolerance and those who are apparently controlled by diet alone.

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Introduction

The management of maturity-onset diabetes mellitus has been facilitated in the past 15 years following the introduction of the sulphonylurea group of compounds. The clinical indications for therapy with these drugs are not yet clearly defined, though their use for the control of hyperglycaemia in maturity-onset diabetes is well established.

Tolazamide is a sulphonylurea closely related to tolbutamide (Fig. 1). After injection the biological half-lives of both drugs are similar (about seven hours) (Weaver, 1966). Owing to the slow absorption of tolazamide from the gastrointestinal tract a daily dose of 50 to 600 mg. is usually satisfactory for the control of hyperglycaemia in maturity-onset diabetes mellitus. The hypoglycaemic action reaches a peak between 4 and 16 hours after an oral dose; however, an effect can still be observed for 24 hours. McKendry and Gfeller (1967) reported that the clinical effectiveness of tolazamide was comparable to tolbutamide and that good or excellent control of hyperglycaemia could be achieved in 56% of diabetics. Tolazamide is about seven times as potent as tolbutamide. Doses as high as 1,000 mg. daily have been used without evidence of toxicity (McMahon *et al.*, 1962; Rennie and Anderson, 1963; Grinnell *et al.*, 1964; Weaver, 1966; McKendry and