NON—A, NON—B HEPATITIS: A NEW SYNDROME IN URAEMIC PATIENTS

M M Avram, D A Feinfeld, A C Gan

The Long Island College Hospital, Brooklyn, New York, USA

Summary

One hundred patients on chronic haemodialysis were studied prospectively over one year for evidence of hepatitis and of infection with hepatitis A or B virus. Five patients developed transient elevations of SGPT, accompanied by a consistent pattern of clinical manifestations, including low-grade fever, anorexia, nausea, hepatomegaly, and hypotension during dialysis. None of these patients had a positive test for A or B virus infection. Non—A non—B hepatitis appears to cause a specific syndrome in uraemic patients, and its transmission in a dialysis unit seems unrelated to blood transfusions.

Introduction

Infection with hepatitis B virus is a well-known problem in patients on chronic haemodialysis. This has been ascribed both to the frequent blood transfusions required by these patients and the aerosolisation of virus-containing blood during dialysis.

The development of techniques to detect infection with hepatitis B virus has led to a reduction in post-transfusion hepatitis, but has failed to eliminate the problem. Hepatitis A infection can now also be diagnosed by serological testing. However, attention has recently been focused on a third form of hepatitis in which no apparent infection with either A or B virus can be found. This entity, which is presently called ‘non—A, non—B hepatitis’ has been more and more frequently associated with transfusion therapy [1,2].

In this study, we have looked at a large group of patients on stable chronic haemodialysis for evidence of disease. Our findings indicate that non—A, non—B hepatitis appears to manifest itself in haemodialysis patients as a distinct clinical syndrome.
Materials and Methods

One hundred patients on stable chronic haemodialysis were prospectively evaluated over a one year period from April, 1977 to April, 1978, with respect to symptoms during and in between dialyses. Blood samples were obtained monthly for analysis for evidence of hepatitis and infection with A or B virus. Patients suspected of having hepatitis had weekly testing. Informed consent was obtained from all patients studied.

Tests were done by the courtesy of the New York Blood Centre under the supervision of Drs Wolf Szmuness and Cladd Stevens. Sera were examined for anti-hepatitis-A antibody by the immuno-adherence method [3]. Assay for hepatitis B surface antigen was performed by solid state radioimmunoassay (Ausira-I-125 © Abbott Laboratories) [4]. Hepatitis B antibody was detected by passive haemagglutination [5].

Serum transaminases (glutamic-oxaloacetic transaminase — SGOT; glutamic-pyruvic transaminase — SGPT) were measured by the method of Reitman and Frankel [6]. Serum bilirubin level was determined by the method of Malloy and Evelyn [7].

The serum samples were also examined for antibodies to cytomegalovirus by standard complement-fixation techniques [8].

Results

Five of the patients studied developed 1—4 month episodes of the following constellation of symptoms: nausea, vomiting, weakness, malaise, and low-grade fever. Concomitant with this they had increased frequency of intradialytic hypotensive episodes.

Case Histories

Case 1. F.R., a 64-year-old Hispanic woman with uraemia secondary to polycystic kidneys, began chronic haemodialysis in 1971. She was stable until May, 1977, when she noted epigastric distress and weakness and began to have frequent drops in blood pressure during dialysis. During the following month, she developed nausea, vomiting, abdominal pain, and was admitted in June, 1977 with temperature 101°F. Cholecystography and upper gastrointestinal x-rays were normal. On July, 1977, SGPT had risen from 25 to 104 and subsequently rose to 122. SGOT and bilirubin were normal. Her dry weight decreased by 3 lbs. After 4 months, she was feeling better. Her medications included only vitamins and aluminum carbonate.

Case 2. A.J., a 58-year-old black woman, had been on chronic haemodialysis since 1975 for uraemia due to chronic glomerulonephritis. She was given blood transfusions totalling 4 units in January, 1976 for anaemia, but none before or after. In June, 1977, she was hospitalised for malaise, nausea, vomiting and temperature 100°F. Increasing hypotension during dialysis was noted. Blood cultures
and upper gastrointestinal x-rays were negative. SGPT was 74, and SGOT 40. Over the next month, SGOT rose to 90 and SGPT to 123. Bilirubin remained normal. By July, 1977, she began to feel better, and transaminase levels became normal. However, in September, 1977, she died suddenly at home; this was felt to be an acute myocardial infarction. Medications included only aluminium hydroxide, ferrous sulphate, vitamins, and bisacodyl.

Case 3. Z.J., a 68-year-old Hispanic woman developed uraemia secondary to diabetic nephropathy and began chronic haemodialysis in January, 1977. She did well except for two episodes of acute congestive heart failure secondary to dietary indiscretion, until August, 1977. At that time, she developed nausea, vomiting, fever of 100°F, and had increasing hypotension on haemodialysis. She was admitted to the hospital, where examination showed mild hepatomegaly. Blood, urine, sputum, and stool cultures were negative for pathogenic bacteria. SGPT rose from 20 to 168, then slowly fell to 39 over the next 3 months. SGOT and bilirubin were normal. During the next three months, persistent anorexia led to a 5lb (2.3kg) dry weight loss. By November, 1977, the patient was improved clinically, and SGPT had fallen to 39. At the onset of illness, her medications included only aluminium hydroxide, vitamins and occasional diazepam.

Case 4. M.S., a 70-year-old white man, had been on chronic haemodialysis since 1973 for uraemia due to obstructive nephropathy complicated by uric acid nephrolithiasis. He was well until December, 1977, when he developed weakness, anorexia, abdominal discomfort, and fever of 100°F. He had difficulty maintaining his blood pressure during haemodialysis, although he gained appropriate amounts of weight between treatments. Cardiopulmonary evaluation and repeated cultures were unrevealing. Mild hepatomegaly was noted on examination. SGPT rose to 208 and SGOT to 152, while bilirubin remained normal. By March, 1978, he began to feel better, and transaminase levels returned to normal. Medications included vitamins, aluminium hydroxide, allopurinol, and biweekly injections of nandrolone 50mg.

Case 5. M.R., a 59-year-old white woman, was begun on chronic haemodialysis in 1974 for anaemia caused by chronic glomerulonephritis. She did well except for recurrent anaemia, requiring 2 transfusions a year; the last was in December, 1977. In February, 1978, she noted weakness and anorexia, and lost 5½ lbs (2.5kg) of her dry weight. Shortly thereafter, she developed abdominal discomfort and temperature 101°F. Cultures were negative. SGPT rose from 3 to 952; SGOT from 12 to 1125, and LDH from 135 to 1105. Serum bilirubin remained normal. Over the next four weeks, the patient improved, and her serum enzymes fell to within normal limits. Medications included aluminium hydroxide, vitamins, and occasional acetaminophen (0–4 tablets a week).

Tests on sera from all 5 of these patients for anti-hepatitis—A antibody were all consistently negative. Assays for anti-hepatitis—B antibodies and for hepatitis—B surface antigen were also uniformly negative. There was, additionally, no
serological evidence of infection with cytomegalovirus or Epstein-Barr virus.

Discussion

During the period of study, 5 of 100 patients on stable chronic haemodialysis developed a constellation of symptoms including anorexia and/or nausea, abdominal discomfort, and fever. In addition, four of them had hepatomegaly on physical examination (Table I). These symptoms lasted between one and four months and were invariably accompanied by an elevation in SGPT. Three of the 5 patients had SGOT elevated as well, but all were anicteric.

Despite this evidence of subacute hepatic inflammation, none of these patients had any evidence of infection with the usual hepatitis viruses, A and B, or with the viruses of cytomegalic inclusion disease or mononucleosis. Only one was

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Renal Disease</th>
<th>Total Transfusions</th>
<th>Max. SGPT</th>
<th>Max. SGOT</th>
<th>Symptoms &amp; Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>F.R.</td>
<td>64</td>
<td>F</td>
<td>Polycystic kidneys</td>
<td>None</td>
<td>122</td>
<td>45</td>
<td>anorexia abdominal discomfort fever hepatomegaly</td>
</tr>
<tr>
<td>A.J.</td>
<td>58</td>
<td>F</td>
<td>Chronic GN</td>
<td>4 units</td>
<td>123</td>
<td>90</td>
<td>nausea &amp; vomiting anorexia fever</td>
</tr>
<tr>
<td>Z.J.</td>
<td>68</td>
<td>F</td>
<td>Diabetic nephropathy</td>
<td>2 units</td>
<td>168</td>
<td>35</td>
<td>anorexia nausea &amp; vomiting fever hepatomegaly</td>
</tr>
<tr>
<td>M.S.</td>
<td>70</td>
<td>M</td>
<td>Obstructive Nephropathy Uric Acid Stones</td>
<td>None</td>
<td>208</td>
<td>152</td>
<td>anorexia abdominal discomfort fever hepatomegaly</td>
</tr>
<tr>
<td>R.M.</td>
<td>59</td>
<td>F</td>
<td>Chronic GN</td>
<td>4 units</td>
<td>953</td>
<td>1125</td>
<td>Anorexia fever hepatomegaly</td>
</tr>
</tbody>
</table>

taking a potentially hepatotoxic medication, nandrolone, and this drug tends to cause cholestatic jaundice, not anicteric hepatitis. The five patients thus meet the criteria for non-A, non-B hepatitis as described in other settings [1,2]. Figure 1 shows the course of the hepatitis in these patients: a transient elevation of SGPT lasting several weeks and unaccompanied by hyperbilirubinaemia. This pattern closely resembles that seen by other observers in this disease.
Figure 1. Course of non-A, non-B hepatitis in five patients on chronic haemodialysis as reflected by serum glutamic pyruvic transaminase (see text)

What makes this syndrome unique in our patients is not merely its occurrence in about 5% of a stable haemodialysis population over the course of a year. All of our patients who developed the disease had a consistent constellation of symptoms, including fever, nausea, or anorexia, and gastrointestinal discomfort. The anorexia led to a dry weight loss in all of the patients, ranging from 3–5½ lbs (1.4 to 2.5kg). Of interest is the fact that during their period of illness, all of the patients had increasing frequency of hypotension during haemodialysis, despite an adequate gain in dialysable weight between treatments. Non-A, non-B hepatitis, then, appears to have very specific manifestations in haemodialysis patients.

This entity has been implicated in many cases of post-transfusion hepatitis. It has been estimated that up to 90% of patients who develop hepatitis after blood transfusions have the non-A, non-B variety [2]. However, two of our patients had never received blood, and a third had not been transfused in 18 months. Although the cause (or causes) of non-A, non-B hepatitis remains
unknown, it would appear that the aetiological agent can be transmitted between patients in a haemodialysis unit, as can the hepatitis B virus. Evidence for a transmissible agent in this disease has recently been published [9,10].

In conclusion, it would seem that non-A, non-B hepatitis can be endemic in a population of patients on chronic haemodialysis, producing a consistent set of symptoms related to indolent, anicteric hepatic inflammation. This disease may be a hitherto unsuspected cause of low-grade fever in dialysed patients, and the intradialytic hypotension and anorexia may adversely affect the patients' progress on dialysis. SGPT, the only consistently abnormal liver function test in this disorder, should be tested when these symptoms occur, and serological testing should be done to rule out classical forms of hepatitis.

References


Open Discussion

KLEINKNECHT (Paris) Could you exclude in your patients the effect of any hepatotoxic drug, such as α-methyldopa or some antiarrhythmic drugs? The second question is: did you use in your patients specific hepatitis B immunoglobulin or common gammaglobulin?

AVRAM The answer to the first question is that in fact, one of these patients was on methyldopa and all the others were on pretty much the same standard medication and therefore the various parameters remained the same. In response to the second question it was hepatitis-specific gammaglobulin. A high titre specific globulin was the most effective, as published in February 1978 in the Journal of Infectious Diseases. However, we are involved now with clinical trials of vaccination with a formaldehyde-killed hepatitis virus.

BURCK (Kiel) Three questions; have you concluded that perhaps the way of infection was from patient to patient? Was there a time correlation between the 5 patients you have observed? One of your patients died from other causes, what was the autopsy report of the liver? Could you find any specific lesion in the liver, because he died three months after he got infected? Thirdly, three of your patients had transfusions. Could you follow up the donor of the blood of the transfusions? Had they similar symptoms in the prior time?

AVRAM In fact, there was a time correlation. There were also sporadic cases
and I must say that since then the amount of non-\textit{A}, non-\textit{B} as defined by us anyway has decreased considerably, but when it does occur it does so in clusters. Question no. 2; the patient with myocardial infarction was not autopsied because of lack of family consent and question no. 3, there has been no \textit{A} and no \textit{B} hepatitis in any of the donors. We have tested them and that has not been the case. Recently, which is quite encouraging, there has been some preliminary evidence from several groups that non-\textit{A}, non-\textit{B} hepatitis can be cross transmitted between man and chimpanzees. This should make our future attempts to identify a 'non-\textit{A}, non-\textit{B}' marker easier.

\textbf{MERY (Paris)} I want to say that we had in Paris a very similar experience to Dr Avram. Within a period of seventeen months we have seen five cases among 83 patients which makes a 6\% incidence of hepatitis we thought to be 'non-\textit{A}, non-\textit{B}' by exclusion of drug toxicity and of known hepatitis viruses.

\textbf{AVRAM} It is a source of joy, the similarity of experience you have observed during long term dialysis. But all our patients are relatively asymptomatic, have not died and not all our patients have received blood transfusions. Also the SGPT remains elevated for some four months. However it is interesting how close the American and European experience appears to be.