Liver Disease in Transplanted Patients

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Over the past several years a number of reports have documented liver disease complicating the course of renal transplantation (Hill et al, 1967; Evans et al, 1968; Leski et al, 1969; Sparberg et al, 1969; Torisu et al, 1971; Malekzadey et al, 1972; Zarday et al, 1972). The incidence and the causes of this complication remain uncertain. Leski et al (1969) reported hepatic disturbances in 24% of the patients transplanted at Necker's Hospital. By contrast Woods et al (1972) reporting the causes of death observed after renal transplantation at the Mayo Clinic failed to note hepatic failure. Furthermore the criteria used to diagnose malfunction of the liver have varied from one series to another.

The present study was undertaken to delineate the incidence of hepatic disease in our series of transplanted patients. An attempt has been made to characterise the clinical course and the treatment of hepatic failure. The role played by Australia antigenaemia, hepatotoxic drugs and infections in the development of liver abnormalities have been analyzed.

MATERIAL AND METHODS

Between June 1963 and November 1972, 218 renal transplantations were performed on 195 patients. 26 grafts came from living donors and 192 from cadavers. The 1 year survival was 78% for the living donor series and 71% for the cadaver donor series.

Details of the immunosuppressive therapy have already been published (Troch et al, 1972). It consists basically of azathioprine and prednisolone. Actinomycin C and antilymphocyte serum were used during the first six months in some patients.

Follow-up of patients after transplantation includes, at regular intervals, determination of BSP retention 45 minutes after an iv injection of 5 mg/kg of body weight of the dye, serum levels of glutamic pyruvic transaminase
(SGPT) (normal range 4-40 U/l) and glutamic oxalacetic transaminase (SGOT) (normal range 6-30 U/l), alkaline phosphatase (normal range 2-5 Bodansky units) and bilirubin. From 1970 on, sera were examined periodically for the presence of Australia antigen (Au antigen) by counter immunoelectrophoresis (Pesendorfer et al, 1970).

The present study includes only patients meeting the following criteria:
1. patients followed in our department after transplantation,
2. patients who had survived for more than two months after transplantation.
The total number of patients was 157, 98 males and 59 females. Observations collected in these patients up to March 1, 1973 form the basis of this report.

RESULTS

1. HEPATIC FAILURE

Hepatic failure was assumed to be present when serum bilirubin exceeded 2 mg/100 ml. This complication occurred in 11 patients, 5 males and 6 females, representing an incidence of 7%. It appeared between 2 and 32 months after transplantation. Bilirubin levels ranged initially from 2.1 mg/100 ml to 9.5 mg/100 ml and reached later a maximum value ranging from 2.1 mg/100 ml to 40 mg/100 ml.

A. Evolution and prognosis of hepatic failure

The course of the disease was variable: in 3 cases, azathioprine was interrupted and both bilirubin and SGPT levels returned to normal within 4 to 20 weeks (Figure 1). In 1 case withdrawal of azathioprine resulted in a return of bilirubin to normal whereas SGPT levels declined without reaching normal values; 21 weeks later, both bilirubin and SGPT levels rose again and this patient died in hepatic failure 37 weeks after the onset of jaundice. Finally, in 7 cases, in 5 of whom azathioprine had been interrupted at some time after the onset of hyperbilirubinaemia, hepatic failure progressed relentlessly and led to death within 1 to 20 weeks.

B. The type of jaundice was variable

In two cases, who recovered after withdrawal of azathioprine, SGPT levels remained below 150 U and alkaline phosphatase below 10 Bodansky units. In 5 cases, SGPT levels were also below 150 U but alkaline phosphatase level exceeded 10 Bodansky units. Only one of these patients recovered. In the last 4 cases, all fatal, SGPT and alkaline phosphatase levels exceeded 200 U and 10 Bodansky units, respectively.

C. Pathology of the liver

Liver autopsy material was available in 8 cases. In three of them antemortem-
Figure 1. Evolution of hepatic failure. Note that azathioprine withdrawal resulted in a rapid fall of serum bilirubin level. Au antigen (HAA) was consistently negative. Serum creatinine remained normal for 75 weeks after withdrawal of azathioprine.

Laparoscopy biopsies had been performed. One of the three patients who had recovered from jaundice died 6 years later from coronary heart disease. At autopsy, liver size was normal and microscopic examination revealed a normal liver architecture. Out of the seven patients who died and in whom an autopsy had been performed, one had severe centrilocular cholestasis and hepatic cellular necrosis associated with cytomegalovirus invasion of the liver, two had an enlarged liver with severe cholestatic lesions and four had atrophic livers (< 1200 g), with signs of chronic active hepatitis.

D. Association with a previously contracted hepatitis

During hepatic failure Au antigen was found in 4 out of the 6 cases in whom it had been looked for. It is of interest to note that three of these patients died and were found at autopsy to have chronic active hepatitis. Analysis of the records of the eleven patients during dialysis disclosed hepatitis, as evidenced by an elevated transaminase and/or bilirubin level, in 3 cases all of whom died with lesions of chronic active hepatitis. It should be pointed out however, that 9 of the 11 icteric patients were dialysed before serial testing for Australia antigen was routinely performed in our unit. Therefore the true incidence of Au antigen hepatitis may have been underestimated.
E. Graft tolerance after withdrawal of azathioprine

Azathioprine was interrupted in 9 patients. In none of them was rejection observed despite the fact, that in six patients interruption lasted more than six weeks (mean 82.8 weeks range 7 to 315 weeks). In no instance has azathioprine therapy been subsequently resumed.

2. HEPATIC DYSFUNCTION

Minor hepatic abnormalities were encountered in transplanted patients with a normal bilirubin level.

A. Incidence of Australia antigenaemia

The Au antigen was found in 53 of the 111 patients (48%) in whom the determination was performed. The incidence of infected patients increased as a function of time after transplantation from 35% during the first six months to 54% during the subsequent six months and 63% between 12 and 24 months.

It is of interest to note that antigenaemia was always persistent. Clearly, the high incidence of antigenaemia after transplantation reflects the 54% incidence of Au antigen hepatitis reported in our dialysis unit (De Smyter et al, 1972). In order to confirm this impression the evolution of 31 patients in whom serial determination of Au antigen had been performed, both during dialysis and during the first twelve months after transplantation, was analysed. Fourteen patients with persistent antigenaemia during dialysis remained chronic carriers after transplantation. The Au antigen was never found in ten patients during their time on dialysis. Nevertheless, three of them became positive during the first twelve months after transplantation. Finally, 7 patients who had suffered from Au antigen hepatitis during dialysis, became negative prior to transplantation. One of them became positive again after transplantation. Overall, 4 out of 17 Au antigen negative patients became positive after transplantation, a finding which may reflect either the uncovering of a hidden antigen by immunosuppressive therapy or a denovo infection.

B. BSP retention

Only a BSP retention above 10%, 45 minutes after the injection of the dye, was taken as clearly abnormal. Table I gives the percentage of tested patients who showed an abnormal BSP retention at different intervals after transplantation. It may be seen that during the first three months only 18% of the patients had abnormal BSP retention. This percentage rose after 3 months and stabilised thereafter around 62%.

C. Serum glutamic pyruvic transaminase (SGPT)

Although the normal level of SGPT ranged between 20 and 40 U/l, only
Table I. Percentage of patients with abnormal liver function tests

<table>
<thead>
<tr>
<th>months post T.</th>
<th>0-3</th>
<th>3-6</th>
<th>6-12</th>
<th>12-24</th>
<th>24-36</th>
<th>36-48</th>
<th>&gt; 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSP &gt; 10%</td>
<td>18%</td>
<td>56%</td>
<td>61%</td>
<td>67%</td>
<td>67%</td>
<td>64%</td>
<td>57%</td>
</tr>
<tr>
<td>(17)</td>
<td>(18)</td>
<td>(46)</td>
<td>(49)</td>
<td>(30)</td>
<td>(28)</td>
<td>(21)</td>
<td></td>
</tr>
<tr>
<td>SGPT &gt; 60 I U</td>
<td>18%</td>
<td>27%</td>
<td>30%</td>
<td>29%</td>
<td>24%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>(137)</td>
<td>(68)</td>
<td>(79)</td>
<td>(74)</td>
<td>(52)</td>
<td>(42)</td>
<td>(28)</td>
<td></td>
</tr>
</tbody>
</table>

( ) number of patients in whom the determination was available

values of 60 U or more were taken as clearly abnormal. As demonstrated in Table I only 18% of the patients had initially elevated levels of SGPT. This percentage rose after six months and stabilised thereafter around 26%. A more detailed analysis revealed a clearcut association between BSP retention and elevated SGPT levels. SGPT levels were indeed abnormal in 32% of the patients with an abnormal BSP retention but in only 7% of those without abnormal BSP retention.

D. Correlation between liver function abnormalities and the presence of the Au antigen

Table II shows that retention of BSP occurs more frequently in Au antigen positive patients than in negative subjects (overall 80% versus 41%). Similarly, an elevated level of SGPT was encountered in 36% of the positive subjects versus only 18% in the negative group.

Table II. Relationship between Au antigenaemia and hepatic dysfunction

<table>
<thead>
<tr>
<th>months post T.</th>
<th>0-6</th>
<th>6-12</th>
<th>12-24</th>
<th>24-48</th>
<th>&gt; 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSP retention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Au antigen -</td>
<td>23%</td>
<td>50%</td>
<td>46%</td>
<td>50%</td>
<td>28%</td>
</tr>
<tr>
<td>Au antigen +</td>
<td>50%</td>
<td>83%</td>
<td>100%</td>
<td>86%</td>
<td>76%</td>
</tr>
<tr>
<td>SGPT &gt; 60 I U</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Au antigen -</td>
<td>16%</td>
<td>17%</td>
<td>16%</td>
<td>26%</td>
<td>16%</td>
</tr>
<tr>
<td>Au antigen +</td>
<td>38%</td>
<td>27%</td>
<td>58%</td>
<td>38%</td>
<td>17%</td>
</tr>
</tbody>
</table>

E. Evolution of liver function abnormalities

1. BSP retention: The evolution of BSP retention was evaluated in 35 patients in whom at least three determinations were available over a period of more than 20 months. Changes in BSP retention exceeding 10% were taken into account. BSP retention increased progressively and stabilised in 10 patients, remained stable in 15 and decreased in 5 patients. In the last 5 patients, it showed only transient changes.

2. SGPT: Similarly, the evolution of SGPT levels was followed in 30 patients in whom a minimum of 8 determinations were available over an interval of at least 36 months.
Throughout the period of observation, SGPT levels remained stable, below 60 U in 12 cases and between 60 and 100 U in 2 others. SGPT levels which had been consistently elevated returned to normal in 4 patients (Figure 2). In 9 patients with initially normal values, SGPT levels showed only transient abnormalities. Finally in 3 patients SGPT values remained continuously abnormal between 100 and 500 U without any evidence of liver function deterioration (Figure 2).

DISCUSSION

The present data demonstrate that hepatic failure is a significant cause of morbidity and mortality after transplantation. 7% of the transplanted patients followed for more than two months develop jaundice, whereas hepatic failure contributed to 20% of the deaths occurring more than two months after transplantation.

Similar figures may be calculated from data reported in the literature: if patients with a serum bilirubin level above 2 mg/100 ml or a SGPT level
above 250 U/l are selected, the incidence of hepatic dysfunction is 15.5% in the series of Torisu et al (1971) versus 8.2% in the present one. The incidence of patients with a serum bilirubin level above 2 mg% is 11% in the Malekzadeh et al series (1972) versus 5.7% in our patients. The death rate attributed to hepatic failure ranges from 8.1% (Evans et al, 1968) to 1.5% (Malekzadeh et al, 1972) of all transplanted patients. For the deaths occurring later than two months after transplantation Torisu et al (1971) report an incidence of 6.1%, a figure to be compared with ours of 5.1%.

The cause of hepatic failure after renal transplantation remains a matter of speculation. It appears quite clearly both from the pathological data and from the clinical course of our patients that several factors must play a role. First of all, azathioprine toxicity contributes to hepatic failure as demonstrated by the prompt reversal of liver function abnormalities after interruption of the drug in three cases. It is also likely that the severe cholestasis noted at autopsy in two other cases is due to azathioprine, as similar lesions have been observed both experimentally and clinically (Einhorn & Davidsohn, 1964; Shorey et al, 1968) after administration of 6-mercaptopurine, the active metabolite of azathioprine.

The discovery of cytomegalic virus in the liver of a patient may be related to similar observations made in transplanted patients by Evans et al, (1968), by Fine et al (1972) and by Malekzadeh et al (1972). The analogy between the observed lesion and those reported in other cases of well documented hepatitis due to cytomegalovirus (Tohill et al, 1967) suggest that cytomegalovirus infection may result in hepatic failure after transplantation.

The lesions of chronic active hepatitis encountered in four cases raises the possibility that previously contracted Au antigen hepatitis may lead to hepatic failure. This interpretation is suggested by the fact that in each case either a history of hepatitis during the time on dialysis was elicited or the Au antigen was present at the time of the icterus.

Azathioprine withdrawal appears to be the sole therapeutic indication to be advised in cases of hepatic failure with functioning renal transplants. Indeed recovery from icterus was noted only in patients in whom the drug had been interrupted. Furthermore, the risks of azathioprine withdrawal seem minimal as no rejection has been observed; on the contrary, it is quite remarkable to note that creatinine clearance remained normal up to 315 weeks after azathioprine interruption. The reason why patients with liver dysfunction seem to tolerate so well the absence of azathioprine is not clear but has already been commented upon (Hume et al, 1966).

The rarity of severe hepatic lesions offers a sharp contrast with the frequency with which minor alterations of liver function were noted in the present series: 2/3 of the patients had abnormal BSP retention and 1/4
raised SGPT levels. To a large extent these abnormalities appear to be related to the presence of the Au antigen. Indeed the frequency of BSP or transaminase abnormalities is twice as high in the Au antigen positive than in the Au antigen negative patients. The interpretation of liver function abnormalities in Au antigen negative cases remains an open question. It might reflect drug toxicity (Haxhe et al, 1967), infection by viruses other than that of Au antigen hepatitis or possibly other infectious agents. Alternatively it may be due to an underestimation of the incidence of true Au antigenaemia in this population because of the insensitive methodology (Torisu et al, 1972).

The prognosis of minor hepatic dysfunction appears to be good. Indeed in none of these patients did hepatic failure develop, a fact which is supported by our observation that SGPT levels had been found elevated within 6 weeks before the development of jaundice in only one out of 9 patients. Furthermore, it should be remembered that hepatic failure was not encountered later than 36 months after transplantation a finding which is unexpected if elevated SGPT levels reflect a slowly progressive hepatitis leading sooner or later to hepatic failure. Finally, the benign prognosis of minor hepatic dysfunctions is borne out by the observation that despite persistently raised transaminase level in several patients for more than 3 years, these values may normalise and not rise again.

SUMMARY

The evolution of liver function is reviewed in 157 patients followed for more than 2 months after transplantation.

Hepatic failure, defined as a bilirubin level above 2 mg/100 ml, was encountered in 7% of the cases. It led or contributed to death in 8 patients. Hepatic failure appeared to be related to azathioprine toxicity and, in some cases, to the evolution of a previously contracted hepatitis. In one case, cytomegalovirus infection seemed to be responsible for liver disease. Reasons for withdrawing azathioprine as soon as hepatic failure develops, are given. Minor hepatic dysfunction was frequently encountered in the other patients. Abnormal BSP retention was present in 2/3 of the patients and elevated serum glutamic pyruvic transaminase level in 1/4 of the patients. These alterations appeared to be associated with a persistent Au antigenaemia.

ACKNOWLEDGMENT

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OPEN DISCUSSION

G SYBESMA (Utrecht): The frequency of Australia antigen positive hepatitis is very high in your patients. Since the frequency with which it is detected depends on the technique, what technique did you use?

van YPERSELE: We used immunodiffusion. Unfortunately I must admit that our dialysis centre has a high rate of hepatitis and that is the reason why the transplant patients have such a high incidence.

P PETERSEN (Denmark): In one of your slides you gave us the incidence of Australia antigen positive patients after transplantation. Could you also
give us the incidence before transplantation. And if so, what was the outcome in these patients as compared with AA-negative recipients? I am interested in this because in our series which is about the same size as yours we have transplanted only one patient with positive AA before transplantation and this patient died two years after transplantation from chronic hepatitis.

van YPERSELE: I cannot answer your question exactly because this series goes back to 1963 and at that time we did not perform routine antigen determinations. So we don’t know what the exact incidence of hepatitis was before transplantation. However, the overall incidence of hepatitis in our dialysis unit is approximately 54 per cent. Several patients we operated on were AA positive before transplantation but that did not seem to carry a bad prognosis. As a matter of fact I tried to hint at least that the hepatic failures we have encountered were not all related to Australia antigenaemia.

PETERSEN: So your conclusion would be that there is no distinction between a patient with positive or negative Australia antigen, related to transplantation and its outcome. Is that your conclusion?

van YPERSELE: It is not a conclusion, but that is what I think. I don’t know it for sure.

M PAPADIMITRIOU (Greece): I should like to ask if you checked serum complement during the negative antigenaemias you had, especially in the first case. It is possible that this was a case of serum hepatitis with a progressive course, and this could have resulted in a negative test. And my second question is, how do these patients die, with coma or a bleeding tendency or what?

van YPERSELE: We have not measured complement serially and the meaning of a negative test, of course, is limited. We have had several patients, not those who died, but who were Australian antigen negative, in whom we could demonstrate the presence of antibodies, so they may have contracted hepatitis but still have been negative at the time of the transplant. That’s one point. It is not answering your question specifically because we don’t have complement measurements. As to your second question: the patients die both in coma and from a bleeding tendency.

V PARSONS (London): I would like to ask as my first question, if the biliary tree, the main branches, was normal. We have had patients with obstructive biliary damage. Was obstruction excluded in all these patients?
van YPERSELE: This was excluded by the appropriate X-ray investigation in the patients who recovered after therapy withdrawal, and by autopsy in all the other patients.

V PARSONS: You did not mention the alkaline phosphatase values in your patients. Was this because this was unhelpful or were they all high?

van YPERSELE: This was because I had only ten minutes for the presentation. It is interesting, but usually the picture is not purely cholestatic. It is always mixed. You have elevated transaminases and alkaline phosphatase in most of the patients but the alkaline phosphatase is usually not very high.

PARSONS: How many of these patients had been on long-term peritoneal dialysis before transplantation?

van YPERSELE: None.

PARSONS: We have one patient with multiple hepatic granulomata and this is stopping us from transplanting him. You did not find it?

van YPERSELE: No.

W ROWINSKI (Warsaw): I would like to ask you whether any of your patients who were Australia antigen negative had been given ALG therapy?

van YPERSELE: During two years we gave ALG to one patient out of two. I cannot answer that question specifically but we could look into it.

ROWINSKI: Do you think that ALG might contribute to liver insufficiency or not?

van YPERSELE: There is no correlation between the damage at least between patients with hepatic failure and those who received ALG. That's certain.

R FINE (Los Angeles): I wonder if you make any adjustments in your other immunosuppressive drugs when you stop azathioprine. In our experience we have had problems in that stopping azathioprine leads to significant impairment of kidney function. I wonder if you use cyclophosphamide when you stop use of azathioprine?

van YPERSELE: No, over the period of time I have reported on, in which I pointed out that there had been no rejection, no substitute was used. As
a matter of fact we have only very recently tried in two of these patients to
switch to cyclophosphamide. One developed a rejection three weeks after
we started cyclophosphamide. I am sure that must be a coincidence.