PART V

TRANSPLANTATION COMPLICATIONS

Chairmen: T Orlowski
           C van Ypersele de Strihou
Role of HBs Antiganaemia in Liver Disease after Renal Transplantation

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Summary

The long-term effect of HBs antigenaemia on patient survival has been evaluated in 121 transplanted patients whose graft had functioned for at least six months. Mortality was significantly higher in the HBsAg-positive (61 patients) than in the HBsAg-negative group (60 patients). Fractional patient survival from six months onwards was significantly decreased at four years in the HBsAg-positive group, as compared with the HBsAg-negative group. Difference in patient survival resulted solely from a fivefold increase in mortality from hepatic disease in the HBsAg-positive group but was unrelated to graft rejection. In some patients, azathioprine withdrawal was associated with improvement of liver disease, whereas reintroduction of immunosuppressive therapy coincided with prompt relapse. HBs antigenaemia did not improve graft tolerance during the first 24 months in 129 patients in whom repeated HBsAg determination had been obtained prior to surgery. It is concluded that prevention of hepatitis might significantly improve long-term results of renal transplantation.

Introduction

Liver disease is a prominent cause of death late after transplantation: in a previous study (Pirson et al, 1973) we have reported that it accounted for 20% of the deaths occurring more than two months after transplantation. The relationship of liver disease to HBs antigenaemia was not evident as a large number of patients had been observed prior to systematic determination of HBs antigen. The present study was undertaken to clarify the role of HBs antigenaemia in the development of liver disease in transplanted patients. The data
demonstrate that HB$_S$ antigenaemia has a deleterious effect on long-term patient survival after renal transplantation. Contrary to previous studies (Brunner et al, 1975; Toussaint et al, 1975; London et al, 1976) no beneficial effect on early graft tolerance was observed.

MATERIAL AND METHODS

From January 1969 through December 1974, 188 transplants were performed on 172 patients and consistently followed by the same staff. Fourteen grafts came from living donors and 174 from cadavers. Immunosuppressive therapy consisted basically of azathioprine and prednisolone. Actinomycin D and antilymphocyte globulin were used during the first six months in some patients (Troch et al, 1972).

Patients' charts were reviewed up to January 1st 1976. In order to assess the long-term effect of HB$_S$ antigenaemia, we analysed the evolution of 121 patients whose graft functioned for more than six months and in whom we had serial liver function tests and repeated determinations of the HB$_S$Ag.

Chronic hepatitis was diagnosed on liver biopsy (five cases) and autopsy sample (one case). Criteria described by de Groote et al (1968) were used to ascertain type and stage of lesion. Diagnosis of cirrhosis relied on biopsy specimen (one case), macroscopic appearance of the liver at laparoscopy (one case) or characteristic biochemical abnormalities associated with prominent features of portal hypertension (four cases). Life table analysis (Cutler & Ederer, 1958) was used to calculate actuarial survival. Differences were tested for statistical significance by Student's t test or by the chi square test.

RESULTS

Effect of HB$_S$ antigenaemia on patient survival more than six months after transplantation

The patients were divided into two groups according to the presence of HB$_S$Ag. As demonstrated in Table I, the number of patients and the mean follow-up period were virtually identical in both groups. By contrast, a significantly higher number of deaths occurred in the HB$_S$ antigen positive than in the HB$_S$ antigen negative group. As a result, patient actuarial survival was poorer in the HB$_S$ antigen positive group. The difference between the two groups appears at 36 months and reaches statistical significance at 48 months (Table II).

Causes of death

The frequency of 'non-hepatic' death was virtually the same in both groups: chronic rejection or complications of anti-rejection therapy (five cases) and
suicide (one case) in the negative group; chronic rejection or complications of antirejection therapy (four cases), sepsis (two cases) and cerebral lymphoma (one case) in the positive group. By contrast, death from hepatic disease was significantly (p < 0.01) more frequent in the positive (10 cases) than in the negative group (two cases).

**TABLE I. Effect of HBsAg on Long-Term Survival**

<table>
<thead>
<tr>
<th></th>
<th>Mortality in the two groups</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number</td>
<td>mean follow-up</td>
<td>deaths</td>
</tr>
<tr>
<td>HBsAg (+)</td>
<td>61</td>
<td>38 months</td>
<td>17</td>
</tr>
<tr>
<td>HBsAg (-)</td>
<td>60</td>
<td>36 months</td>
<td>8</td>
</tr>
</tbody>
</table>

X² : p < 0.01

**TABLE II. Influence of HBs Antigenemia on Survival of Patients Whose Graft Functioned for More Than Six Months After Transplantation**

<table>
<thead>
<tr>
<th></th>
<th>% survival at</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>12 months</td>
<td>24 months</td>
<td>36 months</td>
<td>48 months</td>
<td>60 months</td>
</tr>
<tr>
<td>HBsAg (-)</td>
<td>95 (60)</td>
<td>89 (57)</td>
<td>87 (39)</td>
<td>87 (26)</td>
<td>78 (15)</td>
</tr>
<tr>
<td>HBsAg (+)</td>
<td>93 (61)</td>
<td>88 (56)</td>
<td>79 (47)</td>
<td>64 (29)</td>
<td>59 (17)</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate the number of patients at risk during each period. Difference between the two groups is significant at four years (p < 0.01) but not at five years as a result of the smaller number of patients.

Among the 10 HBsAg-positive patients who died from liver disease (Table III), four acquired the antigen during dialysis and remained positive after transplantation; four were negative at the time of transplantation (two of them had been transiently positive during dialysis) and subsequently seroconverted; for the last two, no information was available prior to transplantation. Of the ten positive patients, six had chronic hepatitis: four cases whose liver biopsy was obtained within the two months prior to death and one case which was autopsied had chronic aggressive hepatitis and chronic persistent hepatitis was found in one case biopsied more than nine months before death (no autopsy). The deaths occurred between 10 and 35 months after transplantation. The four remaining patients died from cirrhosis, between 43 and 60 months after transplantation. The two HBsAg-negative patients died from cirrhosis 30 and 57 months after transplantation. Death resulted from massive digestive tract haemorrhage or liver failure.
<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>HB$_S$ antigenaemia after transplantation</th>
<th>Duration of antigenaemia (months)</th>
<th>Time of death in months after transplantation</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>+/-</td>
<td>5</td>
<td>11</td>
<td>ACH</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>+/- (1)</td>
<td>N.D.</td>
<td>11 (1)</td>
<td>ACH</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>+/-</td>
<td>2</td>
<td>20</td>
<td>ACH</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>+/-</td>
<td>11</td>
<td>35</td>
<td>PCH</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>+/-</td>
<td>1</td>
<td>45</td>
<td>cirrhosis</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>+/- (2)</td>
<td>N.D.</td>
<td>42 (2)</td>
<td>cirrhosis</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>-/+ (7 m)*</td>
<td>3</td>
<td>11</td>
<td>ACH</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>-/+ (4 m)</td>
<td>–</td>
<td>16</td>
<td>ACH</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>-/+ (12 m)</td>
<td>–</td>
<td>34</td>
<td>cirrhosis</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>-/+ (11 m)</td>
<td>3</td>
<td>32</td>
<td>cirrhosis</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>-/-</td>
<td>–</td>
<td>–</td>
<td>cirrhosis</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>-/-</td>
<td>N.D.</td>
<td>–</td>
<td>cirrhosis</td>
</tr>
</tbody>
</table>

(1) first determination of HB$_S$Ag on the 2nd month after transplantation.

(2) first determination of HB$_S$Ag on the 18th month after transplantation.

ACH : aggressive chronic hepatitis
PCH : persistent chronic hepatitis
N.D. : not determined
*
: time after transplantation at which HB$_S$Ag became positive
Effect of azathioprine withdrawal

Azathioprine was withdrawn in 11 of the 12 patients. Withdrawal occurred late in the evolution of the disease in four cases and was followed by death within one month. In the other seven, azathioprine was interrupted as soon as the bilirubin level exceeded 2 mg/dl: prompt improvement in the liver status followed in four, whereas no change was observed in the three others. Despite the initial improvement, the four patients relapsed: one of them within five months, despite definitive azathioprine withdrawal and the three others when either azathioprine (one case) or cyclophosphamide (two cases) was reinstated.

As mentioned in our previous publication (Pirson et al, 1973), interruption of azathioprine was never associated with acute rejection.

Effect of HBs antigenemia on early graft tolerance

In order to assess the effect of antigenemia on early graft tolerance we have selected 129 patients in whom serial HBsAg determinations were available prior to transplantation. In contrast with other studies, no significant difference in graft survival was observed between the positive and the negative group up to 24 months after transplantation: at six and 24 months actuarial graft survival reached 70% and 55% in the negative group versus 76% and 61% in the positive group.

DISCUSSION

The present data demonstrate that HBs antigenemia has a deleterious influence on late patient survival. This effect results solely from an increased incidence of death from severe liver disease. The fact that liver disease develops late after transplantation taken together with the limited number of observations probably accounts for previous reports claiming that HBs antigenemia had no effect on patient prognosis after transplantation. Chatterjee et al (1974) observed 23 HBs positive patients for only 16 months, Shons et al (1974) reported 35 HBs positive patients followed for 21 months, whereas in our group of 61 HBs positive patients, follow-up averaged 37 months.

It is of interest to note that four of the 17 patients who acquired HBs antigen after transplantation died from hepatic failure versus only six among the 44 who were constantly positive. Although this difference is not statistically significant, it raises the interesting possibility that acquisition of the HBs antigen is more deleterious after than prior to transplantation.

The observation that two patients died from cirrhosis despite consistent absence of the HBs antigen underlines the possibility that other agents may cause liver disease such as cytomegalovirus (Fine et al, 1972; Millard et al, 1973; Pirson et al, 1973; Ware et al, 1975) and Epstein-Barr virus (Corey et al, 1975).
As previously demonstrated (Pirson et al, 1973), interruption of azathioprine may be associated with a significant improvement of liver disease. The fact that two patients promptly relapsed after reinstitution of immunosuppressive therapy, either azathioprine or cyclophosphamide, suggests that the degree of immunosuppression might be a more critical factor in the evolution of the hepatic disease than each of these two drugs.

The fact that HBs antigenemia has an unfavourable effect on patient survival late after transplantation is unfortunately not offset by an improved early graft tolerance. Contrary to Toussaint et al (1975), who have observed a significantly better graft survival during the first 24 months in the HBs antigen positive patients, we were unable to detect any difference between the positive and the negative groups. The reason for this discrepancy remains to be determined. Nevertheless, our results strongly suggest that eradication of hepatitis in dialysis units might be an important factor in improving the results of renal transplantation.

Acknowledgments

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Open Discussion

VEREERSTRAETEN (Brussels) We had the opportunity to study a hundred patients, half of whom were antigen negative and half of whom were positive. We noticed that at long term the incidence of liver disease was the same in both groups. We had 3 cases of cirrhosis and 1 death in each group. So, have you any explanation for the difference between your results and ours and have you checked the distribution of other relevant factors within your two groups?

PIRSON Puis-je vous demander quel est le recul pour l'ensemble de la population dont vous me parlez? C'est à partir de trois ans comme vous l'avez vu que la différence apparaît et c'est à 4 ans qu'elle devient significative.

VEREERSTRAETEN Nous avons poursuivi l'étude jusqu'à 3 ans de survie. Il y a 25 à 30% de différence aussi bien pour la survie du patient que pour celle du greffon entre les deux groupes de patients.

PIRSON Il y a bien sûr d'autres causes mais vous avez vu qu'ici pour ce qui est de la relation avec l'antigène de l'hépatite B c'est tout de même à partir de 3 ans que la différence se marque, donc peut-être que le recul doit être un peu plus long pour que cette différence apparaîsse.

WALLS (Leicester) In the UK the incidence of positive antenaemia is decreasing in renal units and I think that this is the second paper we have heard from Belgium today where there has been a significant incidence. The policy in the UK with any such patient would be to institute home dialysis, and by and large, leave the patient there. What I would like to ask is, what is the incidence of positive antenaemia or clinical hepatitis in the medical and nursing staff of either of the two units who presented their data this morning and this afternoon?

PIRSON C'est une fréquence relativement élevée chez les infirmières. Je pense que la moitié, voire les 3/4 de nos infirmières ont fait une hépatite en dialyse.

VERBERCKMOES (Leuven) It may be that the sub-groups of antenaemia are different in Brussels and in Leuven, has anybody tested that? It may be a difference in the aggressiveness of the virus.