ANTI-HLA IMMUNISATION IN 130 HAEMODIALYSED PATIENTS

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Summary

Anti-HLA immunisation has been studied in 130 patients treated by haemodialysis between 1969 and 1978. Until 1977 blood transfusions were restricted (number of transfusions per patient averaged 3.42 units). However 50% of the patients were found to be immunised. The frequency of immunisation was higher in women patients (63%) than in men (39.7%). This difference shows a good correlation with the frequency of pregnancies ($r = 0.849$). The percentage of immunisation increases in parallel with the number of months of dialysis ($r = 0.95$). The capacity to eliminate HB$_S$ Ag seems to be related to the capacity for anti-HLA immunisation: 64% of the patients transiently positive for HB$_S$ antigen develop anti-HLA antibodies and only 26.7% when antientaemia is persistent.

Since 1977, 24 patients have been transfused with two units of whole blood once a week for three weeks, every six months. Antibodies appeared in only seven of them who had been transfused some years ago. The GLA system and transplantation play a small part. The age and the type of nephropathy seem to have no effect. A few patients developed antibodies for no apparent reason. Possibly bacterial or viral infections, or venous allografts were responsible.

Introduction

Until 1977, blood transfusions were often restricted in chronic dialysis patients in order to prevent HLA immunisation. However, in our unit, 50% of the dialysed patients developed anti-HLA antibodies. We have tried to understand the main reasons for this antibody production by looking at different factors and comparing the results with those observed with a new transfusion policy applied during these last 18 months.
Patients and Methods

One hundred and thirty patients with severe chronic renal insufficiency were haemodialysed between January 1969 and December 1978: 57 women and 73 men. The mean age was 44 years, with a range from 15 to 69 years.

Initial nephropathy was glomerular disease (36.30%); interstitial nephritis (24.30%); arterial sclerosis (12.90%); polycystic disease (19.30%) and in 7.2% of cases the nephropathy was of unknown origin.

Anti-HLA antibodies were looked for every two months. Humoral antiplatelet antibodies were sought until 1976 by a complement fixation method but the results were so poor that we have discontinued this test.

Among the different factors which could be responsible for the production of the humoral antibodies, we considered as possibly important and investigated the following: age, sex, number of pregnancies, type of nephropathy, ABO blood group, histocompatibility antigens, duration of dialysis, reaction to HBs antigen, transplantation and blood transfusions.

Results

Sixty-five patients (50%) developed antibodies; they will be referred as Ab+. In 25 of them antiplatelet antibodies were also present.

Age There is no influence of age, which was similar for the Ab+, 45.4 ± 12.4 years, and for the Ab− (in whom no antibodies developed), 45.4 ± 13.2 years.

Sex It is evident that women develop antibodies more frequently; 36 women (63.1%) versus only 29 men (39.7%) (p < 0.05).

Number of pregnancies There were 3.68 ± 0.68 pregnancies in the Ab+ group and only 2 ± 0.41 in the Ab− group (p < 0.05). Moreover, we found a linear relationship between the percentage of immunised women and the number of pregnancies.

Initial nephropathy There was no influence of the type of initial nephropathy.

ABO groups 8.9% of the Ab+ patients were of group B versus O in the Ab− (p < 0.05).

Histocompatibility antigens There is a strong predominance of AW32 in the Ab+ patients (12.5%) compared with none in the Ab− (p < 0.02).

Duration of haemodialysis After 12 months of dialysis 25% of our patients were Ab+, but 55% became Ab+ after three years and 69% after five years of dialysis.

 Reactivity to HBs antigen Three groups of patients were defined. Group I: not antigen positive at any time (53 patients) (43.4%). Group II: HBs antigen persistently positive (15 patients) (12.2%). Group III: HBs antigen transiently positive (54 patients) (44.2%).

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It appears that a significant difference arises only in the third group (p < 0.01) with 64.8% of patients Ab+. In group II most patients were Ab- (73.3%). In group I 58.5% were Ab- and 41.5% Ab+.

Transplantation Thirty five patients have been transplanted. Among those with a functioning transplant, only 11% developed antibodies versus 73% in those who rejected their graft.

Blood transfusions Until 1977, the patients received on average 3.42 ± 0.4 units of washed red blood cells. However Ab+ patients had been more transfused, 4.88 ± 0.54 units versus 1.95 ±0.27 for the Ab- group (p < 0.001).

No relationship to the volume of blood transfused is apparent in patients dialysed for the same period of time. In contrast, for a similar quantity of blood transfused, the duration of dialysis appears to be very important: the longer the duration the more we observe Ab+ patients. For nearly two years we have transfused patients waiting for a kidney transplant with 2 units of whole blood per week for three weeks and repeated the same protocol every six months. Only seven patients among 24 developed antibodies after three transfusions, but they had all previously received a mean of 3 units of blood. The others remained Ab- even after nine blood transfusions (18 units), except five who became transiently antibody positive.

Discussion

Frequency of antibodies in dialysed patients varies from 10.2% [1] to 54.9% [2]. In the thirteenth report of the human transplant registry [3] 28.7% of 3510 patients were immunised. Our result of 50% is high compared, for example, with the France-Transplant* mean figure, 22%. But these results in general concern only dialysed patients waiting for transplantation. If we consider only the patients in our group who are on the transplantation waiting-list, we find that only 33% of them are immunised. Some of our results are identical with those in the literature, for example the frequency of immunisation in women: 30.4% for women and only 19.5% in mean [4, 5]. According to Suarez [6] 45.7% of women are Ab+ versus 23% of men. It seems evident that pregnancies are responsible for this difference: 29% of immunised women have had one or more pregnancies and only 13% had none [7]. For Suarez [6] the difference is greater: 72.7% versus 20%. In the France-Transplant statistics [8] 15% of the women who had one pregnancy were Ab+, with two or three pregnancies 28% and with four, more than 37%.

Even if antibodies are initially absent the rapidity of their appearance after a blood transfusion or a transplantation suggests an anamnestic response. As regards the HLA system, the histocompatibility genes are closely related in the histocompatibility complex to genes which condition the immune response. So the A1B8 patients appear as good responders whereas the A3B7 seem to be bad responders. In our population we have very few A3B7 patients and this may perhaps account for our high percentage of immunised patients. However the significant reactivity of the AW32 which we noted is not reported in the literature. The relationship

* Activity report – 1977 (not published)
between the duration of dialysis and the frequency of immunisation is controversial. According to Lazarus [9], Manzler [10] and Rashid [11] there is no influence, but Mebel [12] and Oh [13] find results similar to ours. Moreover according to Terasaki [7] the risk of immunisation is $0.89 \pm 0.42$ month of dialysis.

The elimination capacity for HB$_b$ antigen seems related to the immunisation faculty in the HLA system. According to Bach [14] there are more anti-HLA antibodies in patients with transient HB$_b$ antigenaemia (62%) than in those with persistent antigenaemia (50%). In our experience this difference is greater, 64.8% versus 26.7%.

With a functional transplant the frequency of antibodies is rare, due to the immunosuppressive therapy and to the fact that true antibodies are fixed on the transplant. In contrast, a high percentage of humoral antibodies is observed after a definitive rejection ranging from 46% [15] to 80% [16]. For Mittal [16] the greater the antigenic difference, the greater the development of antibodies. It is obvious that blood transfusions represent, with pregnancies, the best way of immunisation. The results published are not all identical: for France-Transplant 19% of patients who received less than ten units of blood develop antibodies, from 11 to 40 transfusions, 29% are immunised, and 61% after more than 40 blood units. The results are nearly the same for Tongis [17] and Opelz [18] who found 16% of antibodies after one to five transfusions and 23% after more than five blood units. According to Perkins [19] 30% of patients are spontaneously immunised without any transfusion. With one to ten units of blood he observed 41% of Ab+, 58% after 11 to 20 blood units, and 85% after more than 20. It is certain that the nature of the blood transfused influences the immunisation. However antibodies may develop without any apparent reason. We have observed this fact in two men, in keeping with Manzler [10], Perkins [20] and Salaman [21].

Several hypotheses may be proposed. Antibodies could be cold lymphocytotoxins reacting against non-HLA specificities, but the temperature at which they are in evidence (20–22°C) is against this explanation. Other hypotheses are a cross reaction between a viral or bacterial antigen and an antigen of the HLA system, as has been described for the M protein of some streptococci [22], antibodies related to the venous or arterial allograft [23] or monoclonal proliferation, benign or malignant.

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