PREVALENCE AND CAUSES OF HYPERTENSION LATE AFTER RENAL TRANSPLANTATION

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Summary

We analysed the prevalence and causes of hypertension in 77 patients followed ≥ 7 years after renal transplantation.

Prevalence of hypertension remains stable, around 55 per cent, up to 11 years post-transplant. Age, sex, type of original nephropathy, graft source or prednisolone dosage are not related to hypertension; body weight is greater in hypertensive patients. Presence of native kidneys is responsible for hypertension in about one-quarter of non-nephrectomised patients. No renal artery stenosis was observed in this group. At seven years, serum creatinine is greater in hypertensive patients, suggesting that graft dysfunction is an important cause of hypertension in long term survivors.

Introduction

Owing to the improvement of the results of renal transplantation, an increasing number of patients are presently alive with a long term functioning graft. This population develops several complications potentially more critical for survival than graft tolerance itself. Cardiovascular disease appears to be one of the most important causes of morbidity and mortality in these patients [1–3].

Among the different pathogenic factors implicated in cardiovascular disease, two are of special interest in transplantation: disturbances in lipid metabolism [4] and arterial hypertension [5–7].

The present study was undertaken to determine the long term prevalence of hypertension after renal transplantation and to analyse its cause.

Patients and methods

Seventy-seven patients (44 males, 33 females) transplanted between 1965 and 1974 at the Université Catholique de Louvain (UCL) and the Université Libre
de Bruxelles (ULB), whose graft had functioned for at least seven years were reviewed.

Hypertension was defined as a supine diastolic blood pressure (mean of the five last determinations) \( \geq 90 \text{mmHg} \) in the absence of hypotensive drugs and \( \geq 85 \text{mmHg} \) in the presence of one or more such drugs.

Patients were analysed at the end of eight periods (3, 12, 24, 36, 48, 60, 72 and 84 months) and grouped according to the presence or absence of hypertension at each considered time interval. Patients included in each group may thus vary from period to period.

Permanent characteristics, such as age, sex, nature of original kidney disease, graft source were compared at three months between hypotensive and normotensive patients. Variable characteristics, such as weight, prednisolone dosage and serum creatinine were compared at 3, 48 and 84 months. The analysis of the role of the native kidneys was restricted to the 35 patients grafted at the ULB, as in this series the distribution between binephrectomised (15 patients) and non-nephrectomised (20 patients) subjects was comparable, whereas in the UCL series most patients were anephric.

Immunosuppressive therapy included azathioprine (1.5–3mg/kg/d) and prednisolone (0.15mg/kg/d). Rejection episodes were treated by a transient increase of prednisolone, sometimes associated with antilymphocyte or antithymocyte globulins.

The statistical methods used for qualitative parameters are the \( \chi^2 \) test or Fisher's exact test when one or more values of the contingency tables are smaller than five. For quantitative parameters variance analysis (F test) was utilised.

Results

Long term prevalence of hypertension

The prevalence of hypertension in the 77 patients remains stable: 64, 56, 52, 48, 60, 51, 53, 56, 60, 45 and 50 per cent at respectively 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11 years after transplantation.

Aetiological factors

1. Age: at three months, mean age of hypertensive patients (31.4 ± 1.9, range 7–54 years) is virtually identical with that of normotensive patients (32.7 ± 1.9, range 9–60 years).

2. Sex: hypertension at three months is unrelated to the sex of the recipients, being present in 23/44 males and 14/33 females.

3. Original kidney disease: there is no relationship between the type of original nephropathy and the presence of hypertension at three months. This conclusion is not modified if binephrectomised patients are excluded.

4. Source of the graft: 10 of the 77 patients received a living related donor graft. Prevalence of hypertension at three months in this sub-group (6/10) does not
differ from that observed in the cadaver graft recipients (31/67). Separate analysis of the binephrectomised and the non-nephrectomised recipients leads to the same conclusion. However, the small size of the living donor graft sub-group limits the significance of this analysis.

5. Prednisolone dosage: as shown in Table I, the mean prednisolone dosage is virtually the same in the hypertensive and normotensive patients at 3, 48 and 84 months after transplantation.

<table>
<thead>
<tr>
<th>Months post transplant</th>
<th>Prednisolone mg/d (m ± SEM)</th>
<th>Body weight kg (m ± SEM)</th>
<th>Serum creatinine mg/dl (m ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive</td>
<td>Hypertensive</td>
<td>Normotensive</td>
</tr>
<tr>
<td>3</td>
<td>25.2±1.0</td>
<td>26.9±1.4</td>
<td>58.3±1.9</td>
</tr>
<tr>
<td>48</td>
<td>10.6±0.3</td>
<td>11.1±0.5</td>
<td>64.4±2.2</td>
</tr>
<tr>
<td>84</td>
<td>10.4±0.6</td>
<td>10.8±0.5</td>
<td>61.7±2.2</td>
</tr>
</tbody>
</table>

*  p < 0.5
** p < 0.01

6. Body weight: as demonstrated in Table I, mean body weight at three months is not different between the two groups; however, it is higher in the hypertensive group than in the normotensive group 48 and 84 months after transplantation, the latter difference being significant.

7. Graft function: Table I presents mean serum creatinine in hypertensive and normotensive patients 3, 48 and 84 months after transplantation. It appears that serum creatinine increases in the hypertensive group, the difference with the normotensive group being significant at 84 months (p < 0.02).

8. Native kidneys: the role of the native kidneys was analysed by comparing the prevalence of hypertension among the binephrectomised and non-nephrectomised patients transplanted at the ULB (see Patients and methods).

The prevalence of hypertension averages 65 per cent in the non-nephrectomised subjects versus 50 per cent in the binephrectomised patients (p < 0.01); this difference remains unchanged throughout the seven years of follow-up.

9. Renal artery stenosis: no renal artery stenosis was found in any of the 77 patients. It is however important to note that arteriography was not systematically performed in our patients. In order to evaluate the prevalence of this as a cause of hypertension, we reviewed separately the arteriographies performed in patients transplanted at the UCL between April 1977 and October 1981. Among these 463 patients, 42 underwent arteriography because of hypertension resistant to
usual drug treatment. Renal artery stenosis (defined as > a 50 per cent reduction of the arterial lumen) was observed in 21 cases, i.e. a prevalence of 4.5 per cent.

Discussion

Our data confirm the high prevalence of post transplant hypertension [5, 8]. They further demonstrate the stability of this prevalence up to 11 years after transplantation. This observation is at variance with that of Pollini et al [7] who report a decrease in the prevalence of hypertension between two and four years after transplantation. This discrepancy may result from the fact that Pollini et al [7] analysed a smaller population from which patients with diminished renal function had been excluded.

In agreement with others [9] we found no relationship between hypertension and the age, the sex and the type of original nephropathy. No difference in the prevalence of hypertension between cadaver and living donor graft recipients was found in the present study, but the small size of the latter group limits the significance of this observation. In another study of 65 transplanted children, we observed a significantly higher prevalence of hypertension in cadaveric donor recipients compared to parental donor recipients [10]. Similarly, Jacquot [11] and Curtis [12] reported a lower incidence of hypertension in living donor recipients than in those transplanted with a cadaver graft. It appears thus that the source of graft may influence the prevalence of post transplant hypertension: the better tolerance of the living donor graft probably accounts for this effect [10]. Although high doses of prednisolone are now to be associated with hypertension, the role of the lower doses used later after transplantation remains controversial. The lack of difference in the prednisolone dosage between hypertensive and normotensive subjects in our study argues against a significant aetiological role of steroids in late post transplant hypertension. Other studies have reached similar conclusions [7, 9].

A clear relationship between obesity and hypertension [13] has been proved in non-transplanted subjects. Short-term studies have demonstrated a relation between weight gain and hypertension after transplantation [7, 11]. Our data extend these observations since body weight is significantly higher in hypertensive than in normotensive patients seven years after transplantation. These results draw the attention to the importance of body weight control in transplanted patients. The role of native kidneys in post transplant hypertension has been well documented in previous studies [8, 9, 14, 15]. Our study further shows that the difference in the incidence of hypertension between binephrectomised and non-nephrectomised patients remains constant throughout the seven years of follow-up, suggesting that native kidneys retain their hypertensive properties despite their progressive atrophy. The frequency of this cause of hypertension may be evaluated from our study: the fact that 50 per cent of the binephrectomised subjects are hypertensive suggests that the native kidneys are responsible for the hypertension in 15 of the 65 per cent non-nephrectomised hypertensive patients, i.e. in 23 per cent of them.

Impaired graft function appears to be an important cause of post transplant hypertension, as indicated by the progressive rise in serum creatinine in hyper-
tensive patients, compared to normotensive patients. This is in keeping with two of our previous observations. We reported [5] that the number of patients resuming haemodialysis during the first three post-transplant years is significantly higher in the patients who were hypertensive three months after the operation than in those who are normotensive at this time. As already said, children transplanted with a parental kidney have a lower incidence of hypertension than those transplanted with a cadaveric graft: that this is related to a better graft tolerance is indicated by a lower incidence of early rejection crises and a better graft survival in recipients of parental grafts [10].

The low prevalence (around five per cent) of renal artery stenosis observed in this study might be an underestimate, as arteriography is not systematically performed. However, it is very close to the prevalence reported in a Scandinavian study on the basis of 367 arteriograms performed in 419 grafts [16]. Nevertheless, these studies do not define the prevalence of renal artery stenosis as a cause of hypertension since there is no necessary relationship between the two abnormalities. They just demonstrate that it is not a frequent aetiological factor.

The possible role of genetic factors either present in the recipient or transmitted by the renal graft itself [17], would be clarified by further studies.

Finally, it is quite possible that in a given patient several mechanisms concomitantly act to raise blood pressure.

References


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Open Discussion

CURTIS (Birmingham, Alabama) You suggest that impairment of renal function is one of the causes of hypertension. Your graphs, however, suggest that it may be a result of the hypertension. How do you sort out whether it is really a result or a cause?

WAUTHIER I think that the renal dysfunction is the cause rather than the consequence of hypertension because serum creatinine rises early after transplantation, a feature unusual for benign nephrosclerosis induced by hypertension.

COHEN (London) I was interested in your data, particularly the relationship of the presence of native kidneys to hypertension. In a study that we did at a time following changing our protocol, whereas we had originally performed bilateral nephrectomy at the time of transplantation, we stopped this and our incidence of hypertension rose. We did a retrospective study after about five years which was reported in the BMJ in 1973 and this clearly showed, like you have demonstrated, a relationship between the continued presence of the native kidneys and the increased incidence of hypertension. In the patients where you have demonstrated a relationship between the presence of native kidneys and persisting hypertension, have you performed any bilateral nephrectomies?

WAUTHIER We have performed two bilateral nephrectomies among our patients and in both hypertension resolved.