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RISK FACTORS ASSOCIATED WITH ASEPTIC BONE NECROSIS FOLLOWING RENAL TRANSPLANTATION

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Summary

The risk factors associated with aseptic bone necrosis in 161 consecutive renal transplants were studied by comparing the 38 patients who developed aseptic bone necrosis (24%) with the remaining 123. Females had a higher incidence of aseptic bone necrosis ($p<0.004$), and post-transplant weight gain was a predisposing factor ($p<0.006$). The probability of patients treated with high and low dose prednisolone developing aseptic bone necrosis was 28 per cent and six per cent respectively at three years ($p<0.01$). Subjects possessing HLA-B8 and/or HLA-B12 were more likely to develop aseptic bone necrosis ($p<0.05$). These results suggest that variations in prednisolone pharmacokinetics, possibly HLA-associated, could explain individual susceptibility to steroid-induced aseptic bone necrosis.

Introduction

While it is generally accepted that aseptic bone necrosis following transplantation is related to steroid therapy, the question of why only a proportion of patients develop it remains. The aim of this study was to look at the risk factors associated with aseptic bone necrosis and see whether individual predisposition to its development is HLA-associated.

Patients and methods

From 1969 to 1980, 254 patients received 292 renal allografts. We reviewed the 161 patients who had functioning grafts at three months, who survived for at least six months, and who had annual radiographic skeletal surveys. There were 98 males and 63 females with a mean age of 33 years (range 16–61). Of the 161 patients, 144 received cadaver kidneys and 17 kidneys from living related donors. Twenty-two patients had two transplants, and three patients

had three grafts. The standard criterion of aseptic bone necrosis was its presence on one or more of the serial radiographs. From 1969 to May 1979 patients were on a high prednisolone dose regimen, receiving either 200mg or 150mg prednisolone on day one tapering to 20mg on day 40. All these patients were also given 1g methylprednisolone i.v. at the time of operation. From May 1979 a low prednisolone dose regimen was used with a starting dose of 20mg prednisolone daily and no i.v. steroid during surgery. Azathioprine was given orally in an average dose of 2mg/kg/day throughout the study. Rejection episodes were treated in both groups by 1g methylprednisolone i.v. in two to four successive days.

The risk factors associated with aseptic bone necrosis were studied by comparing patients who developed aseptic bone necrosis with those who did not with regard to age, sex, original disease, nephrectomy prior to transplantation, duration of dialysis, type and number of transplant, HLA mismatches, duration and level of graft function, weight gain during the first six months post-transplant, serum calcium, phosphate, and alkaline phosphatase at the time of transplantation and one month post-transplant, oral and i.v. prednisolone doses, spontaneous fractures, and HLA-A, B antigens.

Statistical analysis was carried out using a proportional hazards model with stepwise selection of variables, and the incidence of aseptic bone necrosis was estimated using survival data techniques. All computations were done with the statistical computing package BMDP and the Minitab statistical package using an ICL 2976 computer.

Results

Thirty-eight of the 161 patients (24%) developed aseptic bone necrosis. Two of these patients were found at autopsy to have aseptic bone necrosis although their radiographs had shown no abnormality, while the remaining 36 patients had radiological confirmation of 115 lesions. These were multifocal and often bilateral, with the commonest site being the femoral head which was affected in 25 of 36 patients (69%). All lesions of the femoral and tibial shafts, 26 per cent of the lesions in the femoral condyles, and 20 per cent of the lesions in the head of the humerus were asymptomatic. The first radiological sign appeared after a mean interval of 19 months (range 5–75).

The analysis picked up three variables correlating significantly with aseptic bone necrosis, namely, sex, weight gain during the first six months post-transplant and oral prednisolone dose during the same period. There was a higher incidence of aseptic bone necrosis in females than in males (23 of 63 (37%) versus 15 of 98 (15%), $p<0.004$), and affected patients had gained significantly more weight (9.5±5.0kg versus 6.3±4.4kg, $p<0.006$). Table I indicates that with regard to prednisolone as a risk factor, there was an individual predisposition to aseptic bone necrosis, since patients with aseptic bone necrosis in the high prednisolone dose group received significantly more prednisolone than those without aseptic bone necrosis, whereas the difference was not significant in the low prednisolone dose group. Furthermore, patients with aseptic bone necrosis in the low prednisolone dose group received significantly less prednisolone than those without

TABLE I. Oral prednisolone dose (mean ± SD, mg/patient)

	Patients with ABN*	Patients without ABN
High dose prednisolone regimen:	n=35	n=85
0– 6 months post-transplant	5,997±1,828[a]	4,793±1,070[b]
7–12 months post-transplant	3,104± 968	2,753± 848
13–24 months post-transplant	5,051±1,103	4,836±1,161
Low dose prednisolone regimen:	n=3	n=38
0– 6 months post-transplant	3,243± 120[c]	3,050± 474[d]
7–12 months post-transplant	2,532± 496	2,251± 451
13–24 months post-transplant	3,698± 42	3,576± 616

a versus b, $p<0.001$; c versus d, NS: b versus c, $p<0.001$; *=aseptic bone necrosis

aseptic bone necrosis in the high prednisolone dose group. Finally, a relationship was sought between HLA-A and B antigens and aseptic bone necrosis. Separate analyses for males and females showed that the significant variables for males were oral prednisolone dose, HLA-B8, and HLA-B12 (total $\chi^2=11.98$, DF=3, $p=0.0075$), and for females were weight gain, HLA-A Blank, and HLA-B8 (total $\chi^2=18.94$, DF=3, $p=0.0003$). The relative risk of males who possessed HLA-B8 and HLA-B12 developing aseptic bone necrosis was 3.8 and 3.0 respectively, whereas that of females with HLA-B8 and HLA-A Blank was 2.1 and 7.9 respectively (Table II). Under the HLA-A Blank variable are included homozygotes and undetected antigens, and hence the clustering of antigens invalidates its significance.

TABLE II. Association between HLA and aseptic bone necrosis (ABN)

	Males				Females			
	HLA-B8		HLA-B12		HLA-B8		HLA-A Blank	
	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Number of patients with ABN	11	4	8	7	7	16	9	14
Number of patients without ABN	35	48	23	60	7	33	3	37
Relative risk	3.8		3.0		2.1		7.9	

The probability of patients in the low prednisolone dose group remaining free of aseptic bone necrosis was 98 per cent at one year falling to 92 per cent at four years. This compared with 92 per cent falling to 70 per cent in the high

prednisolone dose group at the same times ($p<0.01$). The probability of males with HLA-B8 present remaining free of aseptic bone necrosis was 94 per cent and 70 per cent at one and four years respectively, compared to 98 per cent and 90 per cent of the HLA-B8 negative males at these times while the probability of males with HLA-B12 remaining free of aseptic bone necrosis was identical to that of HLA-B8 positive males. Finally, the probability of females with HLA-B8 remaining free of aseptic bone necrosis was 86 per cent and 54 per cent at one and four years respectively compared to 96 per cent and 85 per cent of the HLA-B8 negative females at these times.

Discussion

The pathogenesis of post-transplant aseptic bone necrosis remains uncertain while reports of the incidence have given a wide range from two per cent to 41 per cent [1,2]. Several authors have looked at some of the possible risk factors in the development of aseptic bone necrosis and often produced contradictory conclusions. The discrepancies in the incidence and risk factors are due at least in part to differences in selection criteria of patients, indications for and extent of radiological screening, duration of follow-up, methods of statistical analysis and therapeutic regimens. Although aseptic bone necrosis has been considered a steroid-induced complication the reports which fail to find a correlation between steroids and aseptic bone necrosis [2–4] outnumber those which do find a positive correlation [1,5]. One reason for this is the fact that most of the studies represent results of one immunosuppressive regimen while another relates to the individual predisposition which exists to the development of aseptic bone necrosis [3,5].

Our study has shown a correlation between steroid therapy and aseptic bone necrosis, while we also found that patients who possessed HLA-B8 and/or HLA-B12 were more likely to develop the complication. Susceptibility to other steroid-induced side effects, such as hirsutism [6], and cushingoid appearance [7] has been found to correlate with decreased prednisolone clearance. Variations in drug pharmacokinetics often depend on environmental and genetic factors. Thus it would be reasonable to speculate that inter-subject variation in prednisolone clearance, possibly HLA-B8 and/or HLA-B12 associated, was the reason for the susceptibility to aseptic bone necrosis which we have observed. Further confirmation of this finding from studies with a larger number of patients would be of interest.

In our study predisposition to aseptic bone necrosis was related to the female sex and post-transplant weight gain and neither of these relationships has been reported before. By contrast, osteoporosis is well known to be commoner and more severe in females than males, and Nielsen found that reduction of bone mineral content was more pronounced in female transplant patients than in men [4]. Also Harrington et al [3] reported that weight bearing joints were three times more frequently affected than non-weight bearing ones and we have also reported this [8]. The susceptibility to aseptic bone necrosis which osteoporosis may induce has been postulated to act through the presence of stress subchondral microfractures at weight bearing joints. These may result in

compression or rupture of small intratrabecular arteries leading in turn to ischaemia and necrosis of the bone [9]. However, this may not be the only explanation as there is evidence of aseptic bone necrosis developing in the absence of trabecular fractures [10].

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