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Growth after renal transplants

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SUMMARY The growth of every child with a bone age less than 15 years who received a first renal transplant between 1975 and 1980 was analysed to determine the growth expectation of children with renal transplants substantially maintained on alternate-day prednisolone. Growth was expressed as a standard deviation score defined as the difference between the standard deviation for height at the time of the transplant and at the end of 1981. Average growth achieved by the 46 children, 41 with functioning transplants, was normal with a mean standard deviation score of $+0{\cdot}7 \pm 0{\cdot}3$ (SEM) for boys and $-0{\cdot}3 \pm 0{\cdot}3$ (SEM) for girls; 25 of the children had accelerated growth. Mean standard deviation scores per year of advance of bone age in 29 children was $+0{\cdot}003$, which suggested no overall loss of growth potential. No difference in growth per year of advance in bone age was detected in children with a bone age less than 12 years at transplant compared with more mature children, but boys with a bone age less than 12 years grew better per year of advance in chronological age; this appeared to be related at least in part to their greater growth deficit at transplant. Glomerular filtration rate, alternate-day prednisolone dose, and level of plasma phosphate did not appear to affect growth in the 11 prepubertal children with functioning first grafts.

The final height achieved by adults who receive renal transplants in childhood is on average 3 standard deviations (SD) less than the mean;[1] many are severely dwarfed. A substantial proportion of this height deficit is caused by the poor growth associated with chronic renal insufficiency either before dialysis is necessary or while being treated by regular haemodialysis,[2] especially if the renal insufficiency is present in infancy.[3] Growth after a successful transplant is better than growth on dialysis[4 5] but inadequate growth is still common.[6 7] Growth appears to be inversely related to skeletal maturation with children whose bone age is less than 12 years at transplant growing better than more mature children;[6 8] in one study 8 children less than age 7 years at transplant showed catch-up growth, whereas only 1 of 16 aged 7–11 years, and none of 76 older than 11 years had accelerated growth.[9] Glucocorticoids administered to prevent graft rejection inhibit growth and this is thought to be dose related;[7] alternate-day administration is associated with better growth;[10–13] other factors that may influence growth after transplant are graft function and persistent hypophosphataemia with phosphaturia.[7]

This study is of 46 children substantially maintained on alternate-day prednisolone 6 months after transplants and followed up in one centre; overall growth achievement and the influence of maturity at the time of the transplant are assessed. The effect of graft function, hypophosphataemia, and steroid dosage is also examined in the few prepubertal children included in the study.

Patients and methods

All 26 boys and 20 girls who received a first renal transplant between 1975 and 1980 and were alive in December 1981 were studied. The bone age at the time of transplant was 15 years or less in each child. The overall policy and survival rates have been published;[4 14] actuarial survivals of first live donor and cadaver grafts were 76% and 65% respectively at 5 years. Prednisolone dosage started at 120 mg/m^2, daily reducing to 20 mg/m^2 on alternate days by 6 months between 1975 and 1978; in 1979 this regimen was changed to 60 mg/m^2 daily reducing to 30 mg/m^2 on alternate days by 6 months.

Height was measured by standard methods[15] and bone age determined from a radiograph of the left hand and wrist.[16] Pubertal staging was assessed according to the method of Marshall and Tanner.[17 18] Height was expressed in SD from the mean of a normal population of the same chronological age;[19] thus the 3rd centile corresponds approximately to -2 SD below the mean. Growth was expressed in relation to the expected growth of a normal child of similar age and gender by the differences in the SD for height at the time of the transplant and the SD in December 1981, the difference in the 2 SD being

termed the SD score.[20] The average growth of a child after the transplant was obtained by dividing the SD score by the elapsed time from the transplant to December 1981 (SD score per year). If growth was related to the advance in skeletal age the height was expressed in SD from the mean of a normal population with the same chronological age as the bone age of the child.[20] Glomerular filtration rate corrected to a body surface area of 1·73 m^2 was determined from the height and the level of plasma creatinine.[21] Differences between groups were analysed by the Student's *t* test.

Results

Details of the 46 transplant children are shown in Tables 1 and 2. The height of the individual children at the time of the first transplant and in December 1981, plotted on centile charts is shown in Figs 1 and 2. Fig. 3 shows the height according to chronological

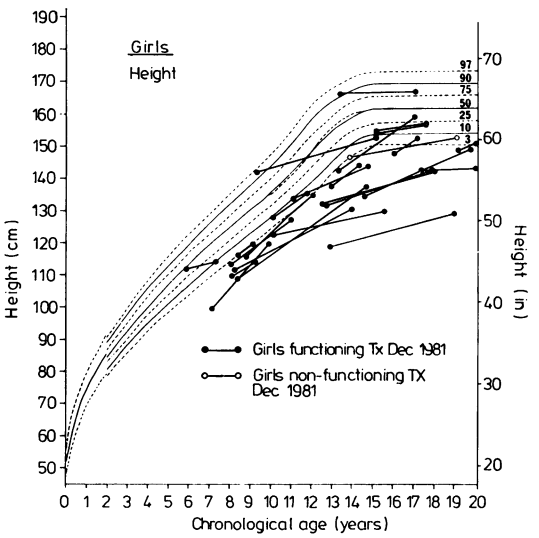

Fig. 1 *Height centiles for girls at transplant and in December 1981.*[15]

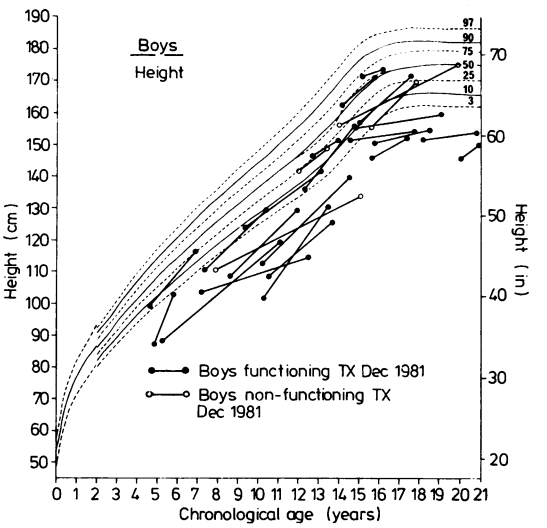

Fig. 2 *Height centiles for boys at transplant and in December 1981.*[15]

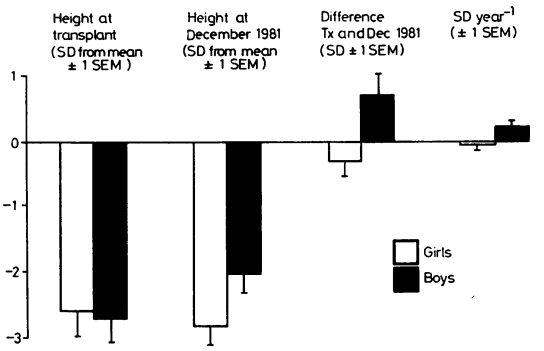

Fig. 3 *Height expressed as standard deviations from the mean of normal population of children of the same chronological age, at transplant and in December 1981. The mean ±1 SEM is shown. The difference (SD score) is shown for the period of analysis and as a yearly change (SD score year).*

Table 1 *Details of boys given transplants, December 1981*

	Number	*Age at transplant (years)*		*Time since 1st transplant (years)*	*GFR ml/min per 1·73 m^2 SA*		*Number of boys*	
		Mean±SD	*Range*	*Mean±SD*	*Mean±SD*	*Range*	*Who were prepubertal*	*On alternate-day prednisolone*
Functioning								
1st transplant	21	11·2±4·1	4·2–18·0	3·1±1·2	58±19	23–80	11	18
2nd transplant	1	15·6	—	2·9	59	—	0	1
Haemodialysis	4	12·1±3·0	7·6–15·4	3·7±2·8	—	—	1	—
Total	26	11·6±3·8	4·2–18·0	3·1±1·5	58±19	23–80	12	19

GFR = glomerular filtration rate, SA = surface area.

Table 2 *Details of girls given transplants, December 1981*

	Number	Age at transplant (years)		Time since 1st transplant (years)	GFR ml/min per 1·73 m² SA		Number of girls	
		Mean±SD	Range	Mean±SD	Mean±SD	Range	Who were prepubertal	On alternate-day prednisolone
Functioning								
1st transplant	16	11·0±3·2	5·8–15·7	3·5±1·7	58±19	23–87	10	14
2nd transplant	3	11·4±1·4	10·1–12·9	3·8±0·6	66±12	54–78	2	1
Haemodialysis	1	13·8	—	—	—	—	0	—
Total	20	11·2±2·9	5·8–15·7	3·6±1·6	59±18	23–87	12	15

age at transplant and in December 1981. Mean SD score for the boys was +0·7±0·3 and for the girls −0·3±0·3 (SEM). Mean SD score per year for the boys was +0·22±0·1 and for the girls −0·01±0·08. A SD score of zero implies normal growth and 25 of the 46 children had positive values showing some acceleration compared with the growth expected.

Bone age determinations at the transplant and in December 1981 were available in 29 of the 37 individuals with a first graft functioning in December 1981. The analysis of height according to bone age is shown in Table 3 which also compares the change in SD score for height according to bone age between boys and girls with a bone age less than, and greater than, 12 years. Mean SD scores per year of advance in bone age for the 29 children was +0·003 suggesting no overall loss of growth potential.

The differences in growth between children with a bone age less than 12 years and greater than 12 years was further analysed by comparing SD scores per year calculated for chronological age and bone age. Only the differences between SD scores per year for chronological age for boys were significant (Table 4). The boys with bone ages less than 12 years had significantly greater height deficits at transplant than the more mature boys (SD −3·6± 1·6 cp −1·9±1·5, $t = -2·8$, P=0·009) suggesting that the better growth of the younger boys might be a consequence of the greater height deficit at transplant. A relationship was therefore sought between height at transplant and subsequent growth. Fig. 4 shows that a significant correlation existed so that the more growth-retarded the child, irrespective of maturity and gender, the better the subsequent growth. A similar but not significant relationship was found between SD scores for bone age and height at transplant.

Sixteen of the 39 children with first grafts which

Table 3 *Analysis of height according to bone age 1st transplants only, functioning at December 1981*

	Number	Mean bone age (years) (mean±1 SD)	SD of height for bone age		SD score of height for bone age (mean±SD)	Time (years) since transplant (mean±SD)	GFR ml/min per 1·73 m²	
			At transplant (mean± 1 SD)	At December 1981 (mean±1SD)			Mean	Range
Girls								
Bone age < 12 years	9	7·3±2·2	−1·3±1·2	−1·4±1·3	−0·1±1·1	3·5±1·9	58	23–77
Bone age >12 years	4	14·0±1·1	−2·2±0·4	−2·1±0·6	−0·01±0·1	2·7±1·0	66	40–87
Boys								
Bone age < 12 years	9	5·8±2·7	−1·4±1·7	−1·3±1·5	0·13±1·7	3·5±1·1	66	23–84
Bone age > 12 years	7	13·7±1·4	−1·1±1·1	−1·4±1·3	−0·3±1·0	2·3±0·9*	57	42–78

* P = 0·041.

Table 4 *Analysis of growth according to bone age and chronological age 1st transplant only, functioning at December 1981*

Bone age	Analysis of growth (mean±1SD)					
	According to bone age SD score per year			According to chronological age SD score per year		
	Girls	Boys	Girls and boys	Girls	Boys	Girls and boys
< 12 years	0·03±0·48	0·11±0·50	0·07±0·51	0·08±0·43	0·57±0·40	0·25±0·53
>12 years	0·02±0·09	−0·08±0·42	−0·04±0·33	0·18±0·16	−0·054±0·29*	0·03±0·28

* P = 0·004.

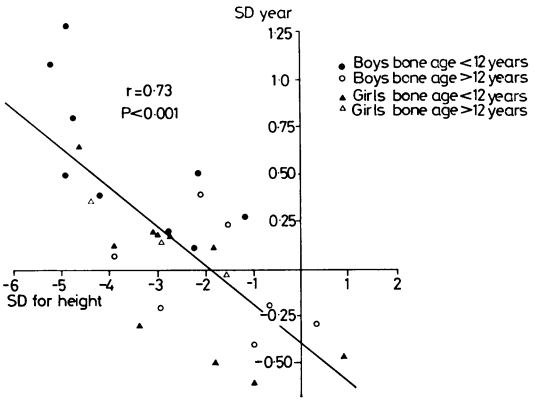

Fig. 4 *Relation between height at transplant (SD for height according to chronological age) and subsequent growth (SD score per year) for children with first transplants.*

were functioning in December 1981 received their graft from a cadaver donor; there was no significant difference in growth between them and those with a live-related donor transplant ($P = 0{\cdot}7$).

Eleven children were still prepubertal in December 1981. All were maintained on alternate-day prednisolone in doses varying from 15 to 34 mg/m^2. Glomerular filtration rate varied between 23 and 84 ml/min per 1·73 m^2, and plasma phosphate levels between 0·91 and 1·65 mmol/l. No significant relation was detected between growth expressed as SD score per year for bone age or chronological age and prednisolone dosage, glomerular filtration rate, or plasma phosphate. Surprisingly, each of the 3 children with a glomerular filtration rate less than 50 ml/min per 1·73 m^2 was receiving more than 30 mg/m^2 prednisolone on alternate days and grew particularly well with a mean SD score per year of +0·8.

Discussion

These results demonstrate that children with transplants can achieve normal growth but while some show accelerated growth, others suffer a further deterioration in height. None the less, the results support the concept that poor growth before transplant has a greater influence on final height[3] than growth after transplant and thus provides some justification for a policy of early transplants in children.[9] There is general agreement that growth is inversely related to steroid dosage and that alternate-day administration allows better growth than the same amount given daily;[7 13] doses as high as 60 mg prednisolone on alternate days have allowed normal growth and absence of deleterious endocrine effects.[10 22 23] However, even though normal growth is possible, catch-up growth may be inhibited particularly during puberty although this seems unlikely if the normal endocrine status of such patients is considered; it is important that the steroids should be administered as single doses, at least 36 hours apart.[23] Other side effects of steroids—such as hypertension—are less common on an alternate-day regimen[13] but some concern has been expressed about an increased risk of rejection.[24] No controlled studies have been carried out but no increase in rejection episodes was detected in a number of surveys in children.[13 11 10] Most children in the present study have been maintained on alternate-day prednisolone with reasonable actuarial graft survival rates at 5 years.[14]

Alternatively some factor other than steroids may inhibit growth in such children; persistent phosphaturia with or without secondary hyperparathyroidism[7 25] has been implicated but no relation between plasma phosphate level and growth was apparent in the few prepubertal children in the present study. Graft function and alternate-daily steroid dosage also did not appear to affect growth. It has been suggested that the longer the period of renal insufficiency the poorer the growth after transplant[9] and that growth retardation in early infancy may limit growth potential.[3] However, no relationship between the period of chronic renal insufficiency before the transplant and subsequent growth was apparent in this study, although it was not possible to make an accurate assessment because of lack of information on renal function before referral in end stage renal failure.

No significant difference in growth was detected between children with bone ages less than, or greater than, 12 years except in the less mature boys in relation to chronological age. It is suggested that the apparently better growth in the children with a bone age less than 12 years may be related in part to a greater degree of growth retardation in the younger children; 10 of the 11 children reported by Ingelfinger *et al.*[9] who were less than 7 years and who grew well, were below the 3rd centile at transplant, whereas only 17 of 52 children 12 years or older and without fused epiphyses who grew poorly were below the 3rd centile. This suggests that growth retardation at transplant may have been a factor in the differences observed though an enhanced effect of steroids on growth in pubertal children or poorer growth potential in older children cannot be excluded.

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