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 +0·7±0·3 (SEM) for boys and −0·3±0·3 (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 +0·003, 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;2 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 dialysis4 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/m², daily reducing to 20 mg/m² on alternate days by 6 months between 1975 and 1978; in 1979 this regimen was changed to 60 mg/m² daily reducing to 30 mg/m² on alternate days by 6 months.

Height was measured by standard methods15 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;10 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.
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termed the SD score. 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. Glomerular filtration rate corrected to a body surface area of 1.73 m² was determined from the height and the level of plasma creatinine.

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 age.

Table 1 Details of boys given transplants, December 1981

<table>
<thead>
<tr>
<th>Functioning</th>
<th>Number</th>
<th>Age at transplant (years)</th>
<th>Time since 1st transplant (years)</th>
<th>GFR ml/min per 1.73 m² SA</th>
<th>Number of boys who were prepubertal (on alternate-day prednisolone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st transplant</td>
<td>21</td>
<td>11.2±4.1</td>
<td>4.2-18.0</td>
<td>3.1±1.2</td>
<td>58±19</td>
</tr>
<tr>
<td>2nd transplant</td>
<td>1</td>
<td>15.6</td>
<td>2.9</td>
<td>2.9</td>
<td>59</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>4</td>
<td>12.1±3.0</td>
<td>7.6-15.4</td>
<td>3.1±2.8</td>
<td>58±19</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>11.6±3.5</td>
<td>4.2-18.0</td>
<td>3.1±1.5</td>
<td>58±19</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate, SA = surface area.
Table 2  Details of girls given transplants, December 1981

<table>
<thead>
<tr>
<th>Number</th>
<th>Age at transplant (years) Mean±SD</th>
<th>Time since 1st transplant (years) Mean±SD</th>
<th>GFR ml/min per 1·73 m² SA Mean±SD</th>
<th>Number of girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st transplant</td>
<td>16 11·0±3·2 5·8–15·7</td>
<td>3·5±1·7</td>
<td>58±19 23–87</td>
<td>10</td>
</tr>
<tr>
<td>2nd transplant</td>
<td>3 11·4±1·4 10·1–12·9</td>
<td>3·8±0·6</td>
<td>66±12 54–78</td>
<td>2</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>1 13·8 — —</td>
<td>—</td>
<td>0 —</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20 11·2±2·9 5·8–15·7</td>
<td>3·6±1·6</td>
<td>59±18 23–87</td>
<td>12</td>
</tr>
</tbody>
</table>

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

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

* P = 0·041.

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

<table>
<thead>
<tr>
<th>Bone age</th>
<th>Analysis of growth (mean±1 SD) According to bone age SD score per year</th>
<th>Analysis of growth (mean±1 SD) According to chronological age SD score per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td>Boys</td>
<td>Girls and boys</td>
</tr>
<tr>
<td>&lt; 12 years</td>
<td>0·03±0·48</td>
<td>0·11±0·50</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>0·02±0·09</td>
<td>-0·08±0·42</td>
</tr>
</tbody>
</table>

* P = 0·004.
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 = 0.7).

Eleven children were still prepubertal in December
1981. All were maintained on alternate-day predni-
solone in doses varying from 15 to 34 mg/m². Glom-
erular filtration rate varied between 23 and 84
ml/min per 1.73 m², 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 m² was receiving more than
30 mg/m² 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
than growth after transplant and thus provides some
justification for a policy of early transplants in
children. 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.28 Other side effects of steroids—
such as hypertension—are less common on an
alternate-day regimen12 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.19 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 phos-
paturia with or without secondary hyperparathyroid-
ism7 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 transplant9 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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References


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