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Growth and height in children after liver transplantation

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Abstract To assess the linear growth after liver transplantation, height curves were constructed for 45 children who underwent liver transplantation at the Children's Hospital "La Paz", Madrid, and were followed for more than 2 years. The prednisolone dose was progressively tapered and switched to alternate-day administration at 12 months. Growth was severely impaired during daily steroid therapy but the mean growth rate normalized in the second year and a significant improvement was observed in successive years. Observations over a long period revealed fluctuating growth rates under stable or decreasing doses of prednisolone on alternate-day administration. Beyond the first year, some annual periods of abnormal growth rate occurred in 57 % of the children. Marginally better posttransplantation growth was observed in children transplanted for intrahepatic cholestatic diseases. The prednisolone dose did not correlate with growth rate. In the long term, short stature was highly prevalent due to an accumulation of factors: previous disease, daily prednisolone period, inconstant growth rate under alternate-day steroid therapy, and pubertal delay.

Key words Statural growth · Liver transplantation

Introduction

Quality of life after liver transplantation during childhood is hampered by the immunosuppressor agents. Their side effects become a main concern when early posttransplantation complications have been successfully overcome and the graft is functioning well. In the long term, infectious diseases and lymphoproliferative disorders are life-threatening but unusual problems. On the contrary, some degree of renal dysfunction and growth impairment occurs in a majority of children. The endocrinological mechanisms underlying the linear growth failure in this population have been poorly studied to date although therapy with glucocorticoids, even in small doses, constitutes an important factor. Knowledge of the features of growth after liver transplantation may lead to a better management of these children.

Methods

Between January 1986 and January 1995, 118 children received a liver graft at the Children's Hospital "La Paz", Madrid, Spain. Forty-five children (27 male and 18 female) were selected for the study of linear growth on the basis of incomplete statural growth at liver transplantation (OLT), absence of vertebral collapse, and a minimum follow-up lasting two years. The mean follow-up was 3.9 ± 1.6 years. Thirty-four children were observed for at least 3 years and 25 patients were followed up for 4 years.

The indications for OLT were biliary atresia in 18 children, intrahepatic cholestasis in 9 (Alagille syndrome $n = 2$, progressive familial cholestasis $n = 4$, neonatal hepatitis $n = 3$), metabolic disease in 13 (alfa 1 antitrypsin deficiency $n = 3$, hereditary tyrosinemia $n = 5$, Wilson's disease $n = 3$, type IV glycogen storage disease $n = 1$, acid lipase deficiency $n = 1$), and other diseases in 5 children (hepatoblastoma $n = 1$, Budd-Chiari $n = 1$, autoimmune hepatitis $n = 1$, acute idiopatic liver failure $n = 1$, cryptogenic cirrhosis $n = 1$). Ten children underwent retransplantation (1 of them twice) for hepatic artery thrombosis ($n = 5$), chronic rejection ($n = 5$), or

Table 1 Prednisolone dose. Values expressed as mg/kg per day. Alternate-day administration beyond 12th month

	6th months	1st year	2nd year	3rd year	4th year
Number of patients	45	45	45	34	25
Mean (± SD)	0.43 (± 0.17)	0.31 (± 0.13)	0.23 (± 0.10)	0.17 (± 0.08)	0.16 (± 0.09)
Range	0.17–1	0.08–0.76	0.05–0.57	0.05–0.5	0.04–0.45

Table 2 Growth velocity after OLT. Values expressed as z score: mean (± SD)

	1st year	2nd year	3rd year	4th year
All	−2.7 (± 2.5)*	◀—▶ −1.9 (± 3.1)	−0.8 (± 2.7)**	◀—▶ 0.4 (± 2.2)
Prepubertal age	−3 (± 1.6)*	◀—▶ −1.6 (± 2.6)	−1 (± 2.5)**	◀—▶ 0.3 (± 1.8)

* $P < 0.01$ ** $P < 0.05$

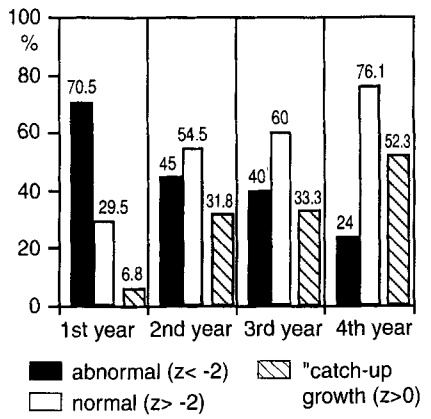

Fig. 1 Patients (%) grouped in categories according to normal (z score > −2) or abnormal (z score < −2) growth velocity after OLT. The *striped column* depicts patients who displayed catch-up growth (z score > 0)

primary non-function ($n = 1$). Their average age at OLT was 6.7 ± 4.2 years, ranging from 6 months to 16 years.

Long-term graft function was normal or showed mild to moderate transaminase elevations, usually linked to chronic HCV hepatitis. Late onset acute rejection episodes occurred in 5 children. Estimated glomerular filtration rate (EGFR) at the end of follow-up was abnormal, range 40–70 ml/min, in 7 patients.

Posttransplant immunosuppression consisted of cyclosporine and prednisolone. Azathioprine was added associated with a lower cyclosporine dose in the 7 cases with compromised renal function. The average cyclosporine dose was 14 mg/kg per day 1 year after OLT and 10.5 mg/kg by the 4th year with mean serum concentrations of 210 and 125 ng/ml (policlonal RIA), respectively. Prednisolone was administered daily during the first postOLT year, at a lower dose during follow-up, and was switched to an alternate-day regime at 12 months. The mean prednisolone dose (mg/kg per day) is detailed in Table 1. Steroid withdrawal was not attempted.

The patients were seen at our outpatient clinic every 3 months. Length or height were measured in a Harpender infantometer or stadiometer. Linear growth rate was assessed annually. The z scores for growth in height and for linear growth rate were calculated according to the following equation: z score = x–mean value for normal/SD for normal, where x is the value for an individual patient and SD is the standard deviation for the normal population of the same age and gender. The z score indicates the number of SDs above (positive value) or below (negative value) the mean for the normal population. Normal reference values for Spanish children were used.

The Student's t-test was applied to determine the differences in the means of unpaired variables. The correlations were evaluated by regression analysis.

Results

Linear/height growth

Mean z score values for growth rate showed severe deceleration during the first year and a normal rate in the following years (Table 2). A significant improvement occurred in successive years, reaching a value slightly over the mean for normal children 4 years after OLT. Nevertheless, while an increasing proportion of children showed catch-up growth, there was a significant group growing below normal limits at each annual evaluation (Fig. 1).

The observation of the patients over along period showed fluctuations in the rate of statural gain. Beyond the first year, under corticosteroid therapy on alternate-day administration, 57 % of the children had at least one annual period with poor growth (z score below-2).

Growth during prepubertal age

Seven male and six female children could be observed over the period of adolescence and seven cases had a delay in the development of secondary sexual characteristics. That feature conditioned low z scores in growth during the period of growth spurt of normal pubertal children, and high z scores during the period in which normal children have almost completed growth. Other cases with a shorter follow-up, limited to the initial stages of theoretical pubertal development, showed absence of pubertal changes.

To exclude artifacts motivated by pubertal delay, linear growth rate was then assessed excluding all data coming from male children more than 12 years old and female children over 11 years old. Differences were noted when results of prepubertal observations were compared with those coming from the older children. There was a worse growth rate during the 1st year (z score:

-3 ± 1.6) and a better z score in the long term (0.3 ± 1.8). By the 4th year 92.2% of prepubertal children grew within normal limits.

Prednisolone therapy and growth

Growth rate was markedly lower while on daily steroid administration in comparison to alternate-day administration. There was no correlation between prednisolone dose and growth rate at any time after liver transplantation.

Previous disease and growth

Patients were assigned to major groups of liver disease, biliary atresia (BA), intrahepatic cholestasis (IC), and metabolic diseases (MD). No significant differences in age at the time of liver transplantation were appreciated (BA: 5.9 ± 3.3 years, IC: 5.1 ± 2.3 years, MD: 7.5 ± 5.2 years). There was no correlation between age and z score for height. Height was particularly decreased in children affected by intrahepatic cholestasis. Before liver transplantation, the z score for height in the IC group was -3 ± 1.9, significantly lower than BA patients (-0.4 ± 1.6) and MD patients (0.1 ± 1.4).

After OLT, higher mean values in z score for growth rate were observed in children previously affected by intrahepatic cholestasis, reaching statistical significance 3 years after OLT when compared with the group of patients who underwent transplantation for biliary atresia (Table 3).

Height

Short stature (z score below –2) was present in 23% of patients at the time of liver transplantation. The height standardized value decreased markedly within the 1st year, 34% of children had a z score for height lower than –2 at that time. There were no statistically significant differences between the z score 1 year after OLT and the score in subsequent years (Table 4). By the 4th year the height was below normal limits in 52% of the children (Fig. 2). Only 15% of the children by the 3rd year and 19% by the 4th year had maintained or improved the z score for height they had before transplantation.

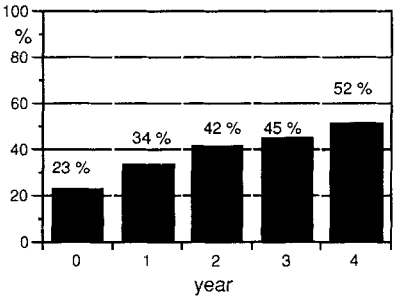

Fig. 2 Patients (%) affected by short stature (z score for height < –2) during follow-up

Discussion

Growth retardation is a sign of malnutrition in children affected by end-stage and cholestatic liver diseases. Short stature before transplantation, as a marker of nutritional derrangement, has been related to higher morbidity and lower patient survival after liver transplantation (4). Recommendations have been made in order to improve nutrition through enteral feeding and to perform OLT at a less-advanced stage of disease. Quality of life in the long term could also be improved by this attitude as features of growth in the present study indicate the difficulty in overcoming a pre-existing statural delay under an immunosuppressor regime including steroids.

Long-term survival is usually associated with satisfactory graft function. Although it was not a requisite for inclusion in the study, liver function tests for our patients were normal or affected by HCV hepatitis without the biochemical signs of choletasis. Rejection episodes had a ready response to treatment. Failure to grow could not be justified by graft dysfunction in any case. Tubular acidosis was detected in 30% of patients but treatment with bicarbonate was established so that acidosis can be excluded as a contributing factor to

Table 3 Growth velocity after OLT according to previous disease. Values expressed as z score: mean (± SD)

	Biliary atresia ($n = 18$)	Intrahepatic cholestasis ($n = 9$)	Metabolic disease ($n = 13$)
1st year	–2.7 (± 2.5)	–2.8 (± 1.3)	–2.7 (± 1.5)
2nd year	–1.6 (± 3)	–1.9 (± 2.3)	–2.2 (± 2.9)
3rd year	–1.7 (± 2)* ◄—►	0.6 (± 2.3)	–0.3 (± 3.4)
4th year	–1 (± 1.9)	0.3 (± 2)	–0.7 (± 2.4)

* $P < 0.05$

Table 4 Z score for height during follow-up

Z score	Pre	1st year	2nd year	3rd year	4th year
Mean	–0.8* ◄—►	–1.6 ◄— n.s. —►	–1.9 ◄— n.s. —►	–1.9 ◄— n.s. —►	–2.3
SD	± 2	± 1.7	± 1.6	± 1.4	± 1.2

* $P < 0.05$

growth retardation. Weight for height was preserved in the majority of patients. Prednisolone treatment is, therefore, considered the main responsible factor affecting growth in these children.

Our results show that corticoid administration on an alternate-day regime restores growth rate to normal mean values. Nevertheless, there were children who did not normalize growth and others who showed fluctuating rates. An explanation for this pattern could not be obtained in view of the absence of correlation between the steroid dose and growth rate. Renal function, assessed by a serum creatinine-based method (Schwartz equation), was no worse in children with growth failure. In some patients, pubertal delay undoubtedly contributed to retarded growth. The cause of the chronic liver disease did not affect postOLT linear growth rate.

Growth was severely impaired in the first postOLT year in this series. Children must grow above normal limits for several years to compensate for this. The achievement of normal growth rate beyond the first year could only maintain the 1-year z score for height.

Cumulated yearly steroid dosage correlated with growth rate scores in the Hannover experience (6). In the experience of the Cochin and Bicetre Hospital, an improvement in the mean z score for height had been achieved 2 years after OLT with respect to the pretransplant value in all the groups of patients established according to previous disease with the exception of the fulminant hepatic failure group (2). Their immunosuppression protocol included a short period, averaging 7 months, of daily prednisolone, and the duration of continuous steroid therapy was inversely correlated with growth rate scores during the first 3 years after OLT. Catch-up growth and improvement of baseline score for height have also been reported in a large group of biliary atresia patients during the 2nd and 3rd post-OLT years (8). On the contrary, another study which switched to alternate-day steroids at 6 months showed progressive retardation in the children's heights, which was below normal limits in 74% of patients after a mean follow-up of 28 months, and a significant correlation between the prednisolone dose and growth was not found (7).

Other alternative approaches to ameliorate growth retardation include steroid withdrawal and growth hormone therapy. Rejection while on monotherapy of cyclosporine has ocurred in 11–13%, but the patients who could be maintained off steroids increased in growth when compared with those on alternate-day steroids (1, 3). The long-term implications of monotherapy are still unknown and further studies are necessary for an appropriate selection of patients. Therapy with growth hormone (GH) could be considered in some patients (8). Reports on the effect of recombinant GH in a short series of children treated with steroids have shown a response inversely related to the amount of prednisone (5).

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