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Long-term Growth of Pediatric Patients Following Living-Donor Liver Transplantation

In order to determine the influence of living donor liver transplantation (LDLT) on long-term growth, we studied the progress of 36 children who had survived more than 5 yr after LDLT from 1994 to 1999. The median age at the transplantation was 1.5 yr (range: 6 months-15 yr) and the median follow-up period was 6.5 yr (range: 5-9 yr). A height standard deviation score (zH) was analyzed for each patient according to medical records. Significant catch-up growth occurred within 2 yr after LDLT with a mean zH changing from -1.2 to 0.0 and was maintained for up to 7 yr post-transplantation (zH-0.1). Younger children (<2 yr) were more growth-retarded at the time of LDLT, but showed higher catch-up growth rates and their final zH was greater than that of older children. Children with liver cirrhosis were more growth-retarded at the time of LDLT, but showed significant catch-up growth and their final height was similar to children with fulminant hepatitis. Growth in children who experienced significant hepatic dysfunction after LDLT was not significantly different from those without graft dysfunction. There was no difference between the types of immunosuppressants used. Our finding suggests that LDLT can result in adequate catch-up linear growth, and this effect can persist even after 7 yr post-transplantation.

Key Words : *Living Donor; Liver Transplantation; Child; Growth*

Seong Jong Park, Sun-Hee Rim, Kyung Mo Kim, Joo Hoon Lee, Bo Hwa Choi, Seon Yun Lee, Soo Hee Chang, Young Joo Lee*, Sung Gyu Lee*

Departments of Pediatrics and Surgery*, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Address for correspondence
Kyung Mo Kim, M.D.
Department of Pediatrics, Asan Medical Center
University of Ulsan College of Medicine, 388-1
Pungnap-dong, Songpa-gu, Seoul 138-736, Korea
Tel : +82.2-3010-3390, Fax : +82.2-473-3725
E-mail : kmkim@amc.seoul.kr

INTRODUCTION

Liver transplantation is the well-established, life-saving therapeutic modality for children with end-stage liver disease. With recent advancements in surgical techniques and immunosuppressive drugs, survival after liver transplantation has improved remarkably since the introduction of clinical transplantation by Starzl et al. 40 yr ago (1-5). Liver cirrhosis in children differs from that in adults because it is frequently accompanied by growth failure (6). Therefore evaluating a child's growth following liver transplantation is used to measure quality of life.

It is well established that liver transplantation results not only in long-term survival, but also in normal growth and development (7-12). However, most of these studies involved cadaveric donor liver transplantation. Therefore we performed this study in order to evaluate the long-term effect of living donor liver transplantation (LDLT) on child growth. We also assessed the influence of other factors on post-LDLT child growth such as the primary diagnosis, pre-transplantation growth retardation, liver graft function following transplantation, and immunosuppressive regimen.

MATERIALS AND METHODS

From a total of 43 children who had undergone LDLT at the Asan Medical Center from 1994 to 1999, 36 children (84%) who had survived over 5 yr were enrolled in this study. Profiles of these children are listed in Table 1. Median age at transplantation was 1.5 yr (range: 6 months-15 yr) and the median follow-up period was 6.5 yr (range: 5-9 yr). Twenty-three of the 36 children underwent LDLT for biliary atresia, 5 for Wilson disease, 3 for fulminant hepatitis of unknown etiology, 2 for unexplained liver cirrhosis, 1 for intrahepatic bile duct paucity, 1 for Byler disease, and 1 for ornithine transcarbamylase deficiency. Seven of the 36 children had fulminant hepatitis. As for the immunosuppressive regimen, 11 children were initially treated with cyclosporin A (CyA) and a low dose corticosteroid while the other 25 children were treated with FK 506.

Follow-up evaluations occurred in 6-month-intervals on an outpatient basis, except during the 1st yr post-LDLT, when check-ups were more frequent. Medical records of pre-transplant and post-transplant examinations were reviewed retrospectively.

For statistical evaluation, a repeated measures ANOVA was used. Data regarding height were expressed as mean height

standard deviation scores (zH). zH was calculated according to the equation: zH=(X-mean height)/standard deviation, where X represents the actual measured height in centimeters and the mean height and standard deviation (SD) represent values of an age- and gender-matched mean height curve from the Korean Pediatric Society Reference published in 1997. Normal growth was defined as zH over -1.5 at the time of LDLT and having the same zH afterwards, essentially staying on the same percentile line for height. Retarded growth at the time of transplantation was defined as zH under -1.5 for the patient's age. Catch-up growth was defined as a gain in zH after LDLT, i.e., crossing the percentile lines for height (13). Lack of growth was defined as a decrease in zH after LDLT.

In order to get an impression of overall growth, we plotted the mean zH versus the number of months post-LDLT for all 36 patients. We then created a homogenous group by selecting 29 of the 36 children who were younger than 6-yr-old at the time of transplantation which eliminated the variation due to pubertal growth spurt. We then examined the influence of pre-transplant growth retardation, primary diagnosis of fulminant hepatitis or chronic cirrhosis, post-transplantation liver graft function, and immunosuppressive regimen.

Table 1. Patient demographics (n=36)

Age	1.5 yr (range: 7 months -15 yr)
Recipient gender	
Male	10 (28)
Female	26 (72)
Diagnosis of 36 recipients	
Biliary atresia	23 (64)
Wilson disease	5 (14)
Fulminant hepatitis	3 (8)
Cryptogenic liver cirrhosis	2 (5)
Intrahepatic bile duct paucity	1 (3)
Byler disease	1 (3)
Ornithine transcarbamylase deficiency	1 (3)
Initial immunosuppression	
Cyclosporine, prednisolone	11 (31)
FK 506	25 (69)

Values are number (%).

RESULTS

Post-LDLT linear growth of all children

Progression of zH, post-LDLT, of all 36 children is shown in Fig. 1. zH values (mean±SD) at the time of LDLT, and 2 and 7 yr after LDLT were -1.2±1.2, 0.0±0.9 and -0.1±1.1, respectively, indicating that there was significant catch-up growth for the first 2 yr and a maintenance of continuous growth in height for up to 7 yr ($p<0.01$).

Post-LDLT linear growth of children under 6 yr of age

A more precise impression of growth post-LDLT is provided in Fig. 2, in which the mean zH is plotted against months post-LDLT for each of the 29 children who were younger than 6 yr at the time of transplantation. By only including children younger than 6 yr, we removed the compounding effect of pubertal growth spurt. zH values at the time of LDLT, and 2 and 7 yr after LDLT were -1.5±1.0, 0.0±0.8 and -0.3±1.1, indicating a similar pattern as was observed for the entire group ($p<0.01$).

Post-LDLT linear growth of patients exhibiting growth retardation at the time of transplantation

zH values (mean±SD) for the 15 children with retarded growth at the time of LDLT, and 2 and 7 yr after LDLT were -2.3±0.6, -0.4±0.8 and -0.8±0.8 respectively, suggesting zH runs to the zero baseline 2 yr after LDLT. It also implies that there was significant catch-up growth within 2 yr after LDLT ($p<0.01$) and the maintenance of continuous growth after catch-up growth in height for up to 7 yr. Furthermore, the zH values for the 21 children with normal growth at the time of LDLT, and 2 and 7 yr after LDLT were -0.4±0.9, 0.4±0.9 and 0.4±1.1, respectively, indicating that there

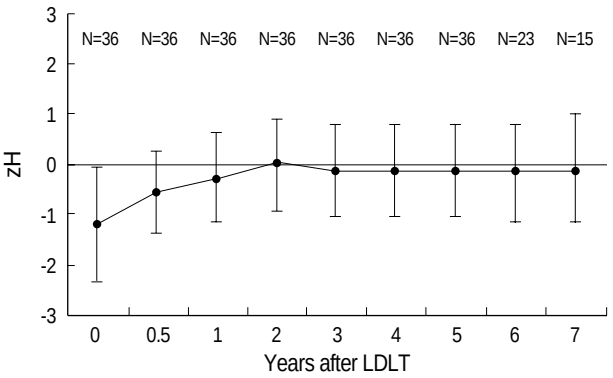

Fig. 1. Post-transplantation mean height standard deviation scores (zH) of all children in the study.

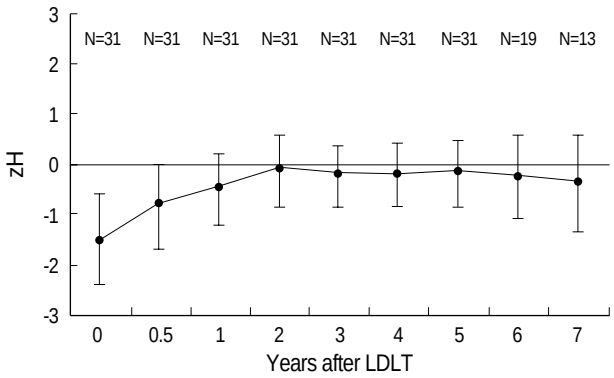

Fig. 2. Post-transplantation mean height standard deviation scores (zH) of children under 6 yr of age at the time of transplantation.

is no stunting of growth after LDLT. The growth gap between the two groups was decreased at 2 and 7 yr post-LDLT from the time of LDLT, but still persisted, indicating that children with retarded growth improve after LDLT, but remain shorter than those with normal growth (Fig. 3).

Post-LDLT linear growth in children with retarded growth according to age

Eleven of the 15 children with retarded growth at the time of LDLT were younger than 2 yr and the remaining 4 were older. zH values (mean±SD) at the time of LDLT, and 2 yr and 5 yr after LDLT were -2.4±0.6, -0.1±0.5 and -0.4±0.7 for the younger group (<2 yr old) and -2.1±0.5, -1.3±1.1 and -1.9±0.9 for older group, respectively. The younger group showed more retarded growth at the time of LDLT, but showed significantly higher catch-up growth after LDLT (p<0.05) (Fig. 4).

Post-LDLT linear growth according to underlying disease at the time of LDLT

The mean zH for children with liver cirrhosis was significantly different from those with fulminant hepatitis at the time of LDLT. The zH (mean±SD) for the 31 children with liver cirrhosis was -1.4±1.2, and -0.1±1.2 for the 5 children with fulminant hepatitis. At 2 yr after LDLT, the mean zH for children with liver cirrhosis was 0.0±1.0, and 0.5±0.5 for those with fulminant hepatitis. After the 2-year follow-up there was no statistical difference between the two groups (p>0.05). This implies that children diagnosed with liver cirrhosis experienced catch-up growth after LDLT, while those with fulminant hepatitis showed maintenance of normal growth after LDLT (Fig. 5).

Post-LDLT linear growth in patients experiencing chronic disease after liver transplantation

Seven of the 36 children experienced chronic diseases after LDLT such as chronic rejection or post-transplant lymphoproliferative disorder. There was no significant difference in the preoperative, 2 and 7 yr post-LDLT mean zH values between children who did and did not experience a chronic disease (p>0.05) (Fig. 6).

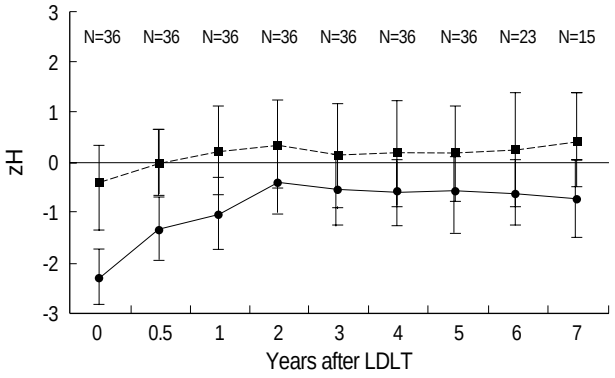

Fig. 3. Post-transplantation mean height standard deviation scores (zH) of children with retarded (●) and normal growth (■).

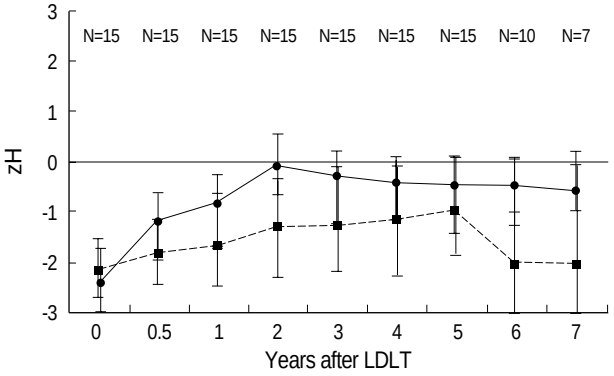

Fig. 4. Post-transplantation mean height standard deviation scores (zH) of children with retarded growth in the younger (<2 yr) (●) and older age (■) groups.

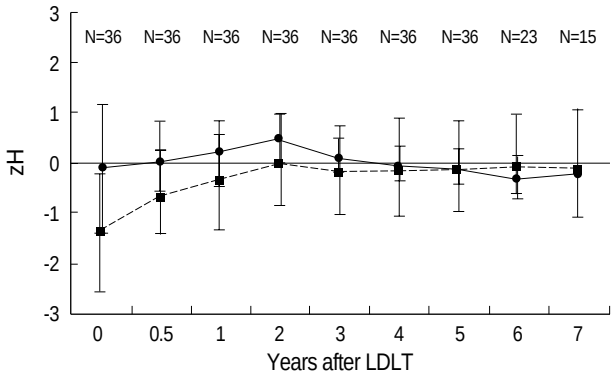

Fig. 5. Post-transplantation mean height standard deviation scores (zH) of children with fulminant hepatitis (●) and liver cirrhosis (■).

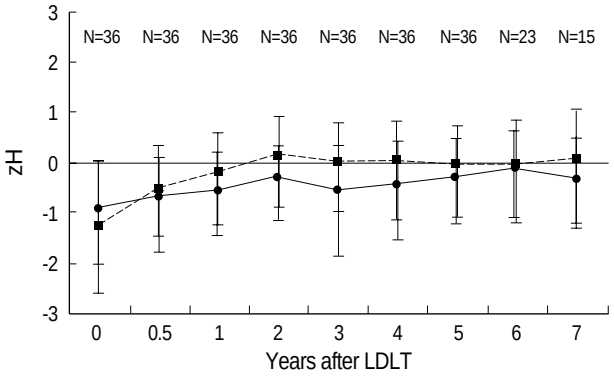

Fig. 6. Post-transplantation mean height standard deviation scores (zH) of children with episodes of chronic graft dysfunction (●) and normal hepatic function (■).

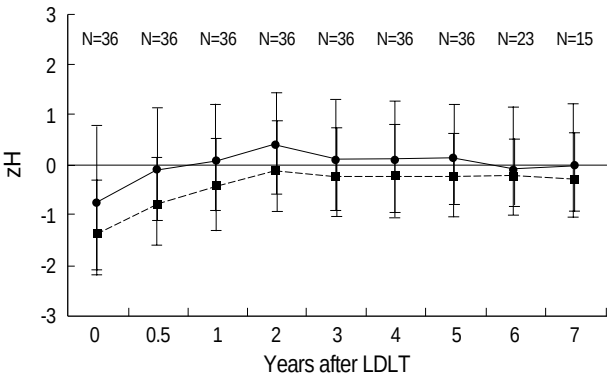

Fig. 7. Post-transplantation mean height standard deviation scores (zH) of children with prednisolone and cyclosporin (•) or FK 506 (■).

Post-LDLT linear growth according to the type of immunosuppression

Eleven children received cyclosporin A and a long-term low dose corticosteroid (CyA group) and the remaining 25 children received FK506 with a short-term corticosteroid (FK506 group). The mean height zH scores for the CyA group at preoperative, 2 and 7 yr after LDLT were -0.8±1.6, 0.4±1.0 and 0.0±1.3, respectively, and for the FK506 group they were -1.4±1.0, -0.1±0.9 and -0.3±1.0. This result indicates that there was no significant difference in linear growth based on the type of immunosuppression (p>0.05) (Fig. 7).

DISCUSSION

The purposes of this study were to investigate post-transplantation linear growth in pediatric LDLT recipients and to examine several variables that may affect their linear growth after transplantation. In comparison to cadaveric donor liver transplantation (CDLT), LDLT has several advantages: it is usually performed electively, it requires a shorter waiting time, the operating environment is superior, and the patient's condition can be controlled better (14-16). Therefore it is hypothesized that LDLT will result in improved linear growth, but only a few studies have investigated its influence (11-17).

We could not compare the linear growth between LDLT and CDLT patients because only two children received CDLT in our center during the study period. The scarcity of cadaveric donors is the largest obstacle for solid organ transplantation in Korea, so LDLT has been vigorously adopted for children since 1994 (5, 18) and expanded to adult patients as well (4).

In our study, children after LDLT improved from a mean zH score of -1.2 at the time of transplantation to -0.1 seven years later. The patients in our study grew to almost normal heights in comparison with their age and sex-matched peers. Contrary to our results, McDiarmid et al. (7) demonstrated in their recent study that even though orthotopic liver transplantation showed some potential for catch-up growth, patients did not achieve normal height (from -1.7 to -1.4). The difference in our findings can be explained by a higher proportion of patients younger than 2 yr in our study (61 vs. 43%) at the time of transplantation. Younger children have shown better achievement of growth in several studies (7, 8, 17). Our findings can be further explained by the advantages of LDLT. The main advantage is its shorter waiting time, which can reverse the effect of chronic liver disease and restore the growth potential of young children. Our children also had a higher zH score (-1.19 vs. -1.72) at the time of transplantation, which can explain the LDLT in a better nutritional status. In a short-term study by Renz et al. (17), they reported that LDLT recipients had better mean zH at the time of transplantation as well as 1 yr after transplantation.

Factors that may affect growth after transplantation can be classified into pre-transplantation and post-transplantation factors. Known pre-transplantation factors are nutritional status, growth retardation (10, 19, 20), age at transplantation (7, 17), and underlying disease (17, 21). Known post-transplantation factors are nutrition, intercurrent illness, impairment of liver function (20, 22), and immunosuppression (23).

As for pre-transplant growth retardation, our study showed that children with pre-transplant growth retardation had higher growth rates than those with normal growth. However, those patients still had shorter heights 7 yr after transplantation. This suggests that children with initial growth retardation have greater catch-up growth (high growth velocity) but the final height correlates with pre-transplant height for the same age group. When these findings were reevaluated according to age, our study showed that catch-up growth was more prominent in patients less than 2 yr old, which has been suggested in several other studies (7, 8, 17). This result suggests that LDLT can be considered for children at young ages who have chronic liver cirrhosis without definite indication for transplantation, but have growth retardation.

Our findings on the influence of primary diagnosis on post-LDLT growth revealed that there was a remarkable difference in the level of the plotted mean zH curves in favor of the group with fulminant hepatitis. Apparently, there was stunted growth at the time of transplantation in children with chronic liver cirrhosis (19) in contrast to children with fulminant hepatitis. An explanation for this difference is the earlier onset of chronic liver cirrhosis and the often more complicated course due to recurrent cholangitis. In contrast, children with fulminant hepatic failure often have good liver function with normal growth before the onset of disease.

Comparing the influence of liver graft function on height shows that poor graft function did not have a negative influence on post-transplantation growth in this long-term follow-up study. This is interesting because our earlier study (24)

and other studies (19-21, 25) have shown that poor graft function has a negative influence on post-transplantation growth. In this study, we excluded children who died within 5 yr after liver transplantation. Therefore most of the children in our study did not have persistent poor graft function. This result suggests that even if children have occasional poor graft function, unless it is persistent, it will not affect height at long-term follow-up.

Our results show there is no difference in growth between the CyA and FK506 groups. Contrary to our results, several earlier reports identified immunosuppression, in particular, the use of steroids, as an additional variable that affects growth after liver transplantation (8, 19, 26). However, each of these previous reports used daily prednisone dosing of at least 5 mg/kg/day. We believe our lower pulse steroid regimen of 2 mg/kg/day with a rapid taper goal of 0.3 mg/kg/day by 1 week post-transplantation and adopting an alternative day regimen as soon as possible, even in children taking CyA, spared our transplant recipients of the negative effects of steroids on linear growth. This effect had been reported in recent studies (7, 10, 17) similar to ours, whereas an older study by Bartosh et al. (8) showed a long-term negative impact of steroids on post-transplantation growth.

Although this was not a comparative study including cadaveric liver transplantation, this study showed that LDLT restored the growth in children with growth retardation by catch-up growth, and preserve adequate growth in non-growth-retarded children for up to 7 yr. Therefore LDLT appears to be a promising modality not only in long term survival, but also in long-term normal linear growth.

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