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Paul M. J. G. Peeters
Egbert Sieders
Elisabeth M. ten Vergert
Theo Kok
Wil Ch.C. Reitsma
Koert P. de Jong
Charles M. A. Bijleveld
Maarten J. H. Slooff

Analysis of growth in children after orthotopic liver transplantation

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Liver Transplant Group
University Hospital Groningen,
The Netherlands

P.M.J.G. Peeters (✉) · K.P. de Jong
M.J.H. Slooff
Department of Surgery,
Division of Hepatobiliary Surgery
and Liver Transplantation,
University Hospital Groningen,
P.O. Box 30.001,
NL-9700 RB Groningen, The Netherlands
Fax: + 31 50 361 4873

E. Sieders · W.C.C. Reitsma
C.M.A. Bijleveld
Department of Pediatrics,
University Hospital Groningen,
P.O. Box 30.001,
NL-9700 RB Groningen, The Netherlands

E.M. ten Vergert
Office for Medical Technology
Assessment,
University Hospital Groningen,
P.O. Box 30.001,
NL-9700 RB Groningen, The Netherlands

T. Kok
Department of Radiology,
University Hospital Groningen,
P.O. Box 30.001,
NL-9700 RB Groningen, The Netherlands

Abstract Growth after pediatric liver transplantation is an important factor in determining the quality of life. We collected data on height, skeletal age, and liver function of 45 consecutive pediatric transplant recipients and assessed the influence of primary diagnosis, liver function, and immunosuppressive regimen on their growth. Height and skeletal age were plotted as median standard deviation scores versus years post-transplantation. Growth, in terms of both height and skeletal age, were continuous without catch-up growth. Primary diagnosis was found to have no influence on height and poor liver function had a negative effect on both height and skeletal growth. A higher alternate day prednisolone maintenance dose also had a negative effect on skeletal growth. Thus, it can be concluded that a pretransplant lack of growth will not be restored and is an indication for early transplantation in end-stage liver disease, especially in younger children.

Key words Growth, liver transplantation, children · Children, growth, liver transplantation · Liver transplantation, growth, children

Introduction

The life expectancy for children with end-stage liver disease or an inborn, metabolic error with its primary defect in the liver has been found to improve substantially after orthotopic liver transplantation (OLT). Nowadays, experienced liver transplant centers report 1- and 5-year patient survival rates of 77 %–89 % [5, 8, 12, 16, 21] and

78 % [5, 30], respectively. Not only survival is important, but also the quality of life after transplantation. Several centers have reported an excellent quality of life after OLT in adults [26]. That after pediatric OLT is less well established since, in very young children especially, the quality of life is much more difficult to assess than in adults. Moreover, in children, additional factors, such as normal growth and a balanced psychosocial and normal neurological development, play an important role in determining the quality of life after OLT.

Lack of growth in children with end-stage liver disease is caused by an impaired intake of food, malabsorption of nutrients and vitamins from the intestine, and a decreased protein synthesis of the diseased liver. These children suffer from fatigue, ascites, and hepatosplenomegaly, which lead to loss of appetite and diminished oral intake. Weight loss and muscle wastage then lead to a vicious circle of anorexia and progressive cachexia. Nutritional intake is impaired due to malabsorption of fat and fat-soluble vitamins (A, D, and E). In addition, as a result of the often longstanding cholestasis, the liver has a poor synthetic capacity [3, 13, 27]. As result of anorexia, malabsorption, and poor synthetic liver function, these children show delayed bone maturation and lack of growth [26, 28].

Restoration of growth and catch-up growth after pediatric OLT are important for good rehabilitation. In order to achieve this goal, nutrition must be adequate, with good resorption of nutrients from the intestine. Moreover, the new liver should have good function. Thus far, little is known about restoration of growth or catch-up growth after OLT in pediatric patients; however, both would appear to be influenced by the patient's age at onset of liver disease, age and bone maturation at the time of OLT, pretransplant lack of growth, performance of the graft, and immunosuppressive therapy [23].

In this study we report our observations concerning growth after OLT in a group of 45 consecutive pediatric transplant recipients who survived for at least 1 year.We also assess the influence of primary diagnosis, liver graft function, and immunosuppressive regimen on growth in a selected group of children who were less than 6 years old at the time of transplantation.

Patients and methods

For this descriptive, retrospective study we selected our first 45 pediatric transplant recipients who survived for at least 1 year. These children were consecutively transplanted between November 1982 and December 1992. The children received either a first or second liver graft. Only patients with early retransplants (i.e., within 3 months) were accepted for this study. Those with late retransplants were censored in order to prevent longstanding interference of a poorly functioning primary graft on growth. The median follow-up time was 3 (range 1–5) years.

Table 1 Patient and transplantation variables

	(n = 45)	(n = 36)
Recipient age (years)	3.1 (0.33–16)	3.0 (0.33–5.92)
Recipient gender		
Male	26 (58 %)	24 (67 %)
Female	19 (42 %)	12 (33 %)
Recipient weight (kg)	12.4 (5.5–63)	10.0 (5.5–18.6)
Recipient diagnosis		
Biliary atresia	24 (53 %)	20 (56 %)
Metabolic diseases	11 (24 %)	9 (25 %)
Cholestatic diseases	9 (20.0 %)	6 (17 %)
Acute hepatic failure	1 (2 %)	1 (3 %)
Graft type		
Full-size graft	22 (49 %)	16 (44 %)
Reduced size or segmental graft	23 (51 %)	20 (56 %)
Immunosuppression		
Aza, prednisolone, CyA	40 (89 %)	32 (89 %)
Aza, prednisolone	5 (11 %)	4 (11 %)

Continuous variables are shown as median values; year (range), kg (range)
Nominal variables are shown as number of patients (%)

Recipient and graft characteristics are listed in Table 1. The severity of liver disease was expressed as the Child-Pugh sum score; 90 % of the children scored in class B or C. In total, 33 out of 45 children (73 %) underwent transplantation for biliary atresia or other cholestatic diseases, 11 (24 %) for primary, inborn, metabolic errors of the liver, and 1 (2 %) for an acute hepatic failure. There were no children with Alagille's syndrome in the cholestatic disease group. Five of the 45 children (11 %) had an early retransplantation. Two children with biliary atresia were retransplanted because of primary nonfunction (n = 1) and persistent poor function (n = 1). Three children with tyrosinemia were all retransplanted because of hepatic artery thrombosis.

The selection of potential pediatric recipients was done according to a strict protocol, as described earlier by our group [17]. Liver transplant candidates were followed up in the pretransplant phase on an outpatient basis. Data on weight, height, liver function, calendar and skeletal age were collected according to a strict time scheme. Depending on the severity of liver disease, suitable candidates were placed on a waiting list and prepared for transplantation.

Liver grafts were selected solely on the basis of ABO blood group compatibility and standardized donor parameters [18]. Full-size matched liver grafts were preferred; however, because of the shortage of size-matched donor organs, reduced-size (right or left liver lobes) or segmental grafts (left lateral segments) were used as well. Twenty-three children (51 %) received such partial liver grafts.Up until 1987, liver grafts were perfused with Euro-Collins solution (n = 12); after that time, University of Wisconsin solution was used (n = 33).

Full-size and reduced-size grafts were transplanted in orthotopic position, as described by Starzl et al. [25] and segmental grafts in piggyback position, as reported by Ringe et al. [19]. Biliary reconstruction was done either by a duct-to-duct choledochocholedochostomy or by an end to side Roux-en-Y hepaticojejunostomy.

Immunosuppression

The first five patients in this study were treated with a conventional, double immunosuppressive regimen consisting of azathioprine (2–3 mg/kg per day) and prednisolone (starting dose 4 mg/kg per day, slowly tapered to a maintenance dose of 0.5–0.8 mg/kg per day). Between 3 and 6 months post-OLT, prednisolone was further tapered to 0.5 mg/kg per day, given on alternate days. In addition to this regimen, cyclophosphamide (3 mg/kg per day) was given during the first 10 postoperative days. After May 1985, patients were treated with cyclosporin A in addition to our conventional regimen, at a starting dose of 4.5 mg/kg per day i. v. When possible, the i. v. administration was converted to oral doses. Dosages were aimed at maintaining trough levels of 200–250 ng/l whole blood during the first 4 weeks and 100–150 ng/l thereafter. With this regimen, the alternate day prednisolone dose was tapered more quickly and to a lower level (0.3 mg/kg per day) than with the conventional regimen.

Clinically evident and histologically proven rejections in the first 4 weeks after OLT were treated with three successive i. v. bolus injections of methylprednisolone, 20 mg/kg per day. After this period, depending on the severity of the episodes, rejections were treated with an increased dosage of oral prednisolone (to a maximum of 4 mg/kg per day for 3 days) and then tapered. ATG and OKT3 were not used in this series.

Patients were followed up at yearly intervals on an outpatient basis, except during the 1st year post-OLT, when check-ups were more frequent. Anthropometric measurements were taken, graft function tests given, and estimation of skeletal age made at each yearly visit.

Anthropometric measurements were routinely taken, with the patient barefoot and wearing only undergarments, at each clinical outpatient visit in the pretransplant phase. The same measurements were subsequently taken at yearly intervals in the post-transplant phase. The height of children up to the age of 2 years was measured with them stretched out flat on a calibrated table; those above this age were measured in the supine position with a wall-fixed stadiometer. Weights were obtained in younger children laying down, and in older children standing, on a scale. For statistical evaluation, data regarding height were expressed as standard deviations scores (SDS).

Standard deviation scores (SDS) were calculated according to the equation: SD score = (X – mean height)/SD, where X represents the actual measured height in centimeters and the mean height and SD represent values of an age- and gender-matched Dutch population. Normal growth was defined as having the same SDS for height both at the time of OLT and afterwards, i. e., staying on the same percentile line for height. Catch-up growth was defined as a gain in SDS for height after OLT, i. e., crossing the percentile lines for height. Lack of growth was defined as a decrease in SDS for height after OLT. In the case of catch-up growth or lack of growth in a single child, the gain or loss would be more than 2 SD [24].

Skeletal age was estimated by comparing an X-ray of the wrist joint with the compiled developmental data of the wrist joint of a normal population, as depicted in the radiographic atlas of skeletal development of the hand and wrist from Greulich and Pyle [10]. All of the wrist X-rays made at yearly intervals in the pre- and post-transplant phases were retrospectively evaluated by the same radiologist (T. K.). The individual data were also expressed as SDS, according to the abovementioned equation, with SD representing values of a skeletal age- and gender-matched population.

Graft function was also evaluated yearly on the basis of two parameters: (1) the presence of cholestasis (bilirubin level) and (2) the synthetic capacity of the liver (cholinesterase level). If both parameters were within normal ranges at consecutive yearly intervals, graft function was judged as being good. If one or both parameters were out of the normal range at one of the yearly intervals, graft function was judged as poor.

Patients (Fig. 1)

In order to get an impression of overall growth, we plotted the mean SDS for height and skeletal age versus years post-OLT for the entire group of 45 children. Then, we created a homogenous group by selecting 36 of the 45 children who were less than 6 years old at the time of transplantation, thereby eliminating the variation in puberal growth spurt. The gender variation in the physiological growth spurts in younger children is smaller than in older children; moreover, older children who have already reached their epiphyseal junction at the time of transplantation do not show any growth in terms of height after OLT. Overall results of growth in this group were also given by plotting the mean SDS versus the years post-OLT.

We then examined the influence of primary diagnosis, liver graft function, and immunosuppressive regimen on growth in a homogenous cohort of 26 pediatric transplant recipients. The inclusion criteria were: age less than 6 years at the time of transplantation and a minimum follow-up period of 2 years. The choice for a follow-up period of 2 years was based on several studies demonstrating catch-up growth for height in the time period from 6 months to 2 years post-OLT [2, 6, 9, 29].

The influence of primary diagnosis on growth was determined by comparing growth after OLT in children whose primary disease was either cholestatic or metabolic, provided they had good liver graft function. The influence of liver graft function on growth was determined by comparing growth after OLT within the two primary diagnostic groups to avoid interference of the primary diagnosis on the growth results. To study the effect of immunosuppressive regimen on growth, we looked at children who underwent transplantation for a cholestatic disease with good liver graft function during the 2-year follow-up period.

To show possible effects of primary diagnosis, liver graft function, and immunosuppressive regimen on growth, the median SDS for height and skeletal age were plotted versus years post-OLT.

Because of the small numbers of patients in the various subgroups, we did not apply any statistical tests.

Results

The overall growth of the 45 transplant recipients is shown in Fig. 2 a, where the median SDS for height and skeletal age versus years post-OLT is indicated. Both curves for height and skeletal age run parallel to each other and to the zero baseline, indicating that there is continuous growth in both height and skeletal age in the long term without general catch-up growth.

A more precise impression of growth post-OLT can be gotten by looking at Fig. 2 b, in which the median SDS for height and skeletal age is again plotted against years post-OLT for the 36 children who were less than 6 years old at the time of their surgery. The course of the curves for height and skeletal age shows the same pattern as that observed in the group as a whole, i. e.,

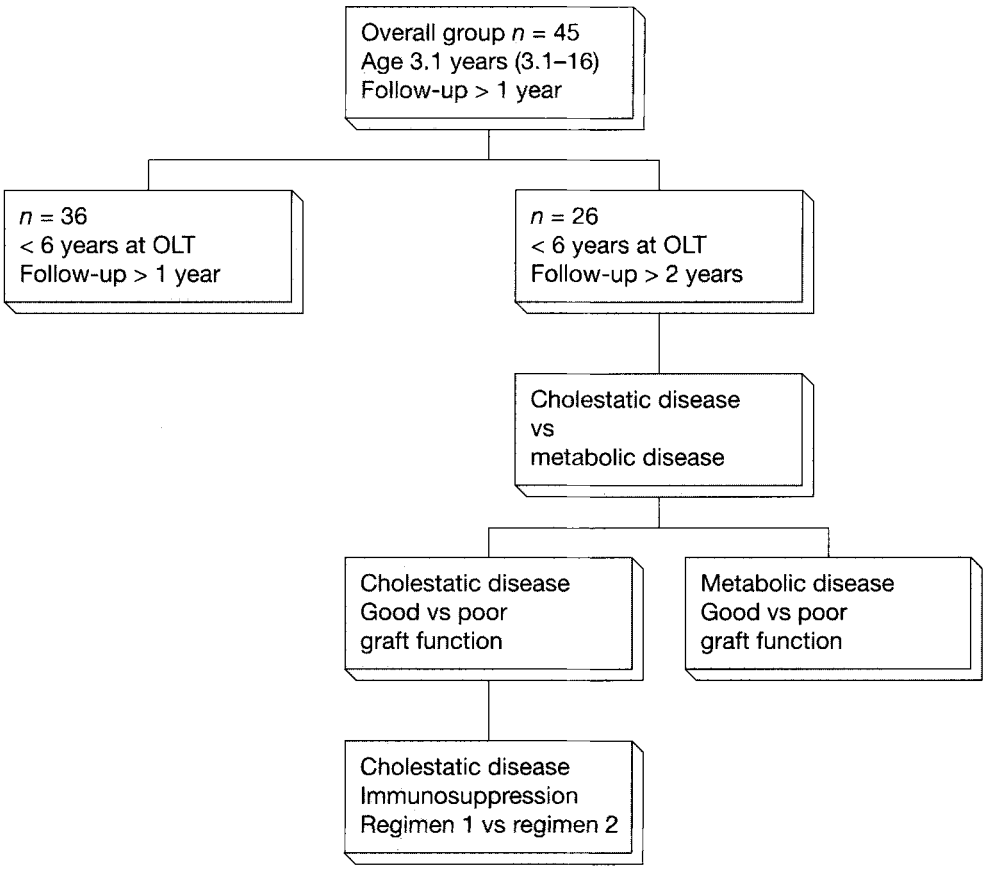


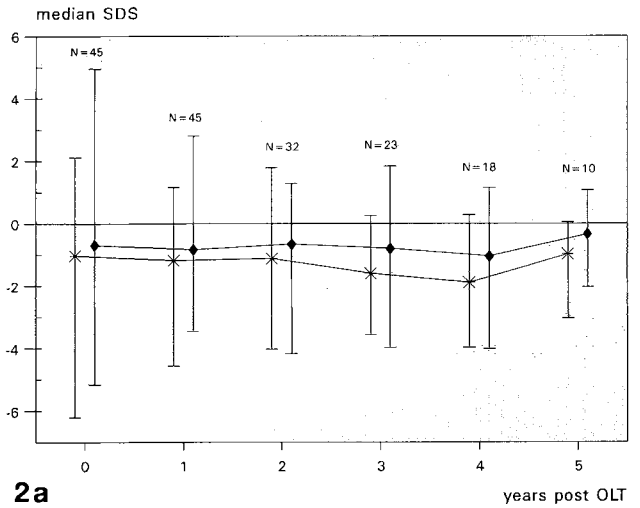
Fig. 1 Study design

also continuous growth of both height and skeletal age without general catch-up growth.

The influence of primary diagnosis, liver graft function, and immunosuppressive regimen on growth was explored in the homogeneous cohort of 26 children and is reflected in Fig. 3. Beginning with the influence of primary diagnosis on height and skeletal growth after successful OLT for cholestatic or metabolic disease in the presence of good liver graft function, the median SDS height curves of both diagnostic groups run parallel, indicating that there is no influence of primary diagnosis on height 2 years after successful transplantation. However, the median SDS skeletal age curves run divergent to each other and to the zero baseline. This means that in contrast to the cholestatic disease group, there is skeletal age catch-up growth of two SDs in the metabolic disease group 2 years after successful transplantation.

As for the influence of liver graft function on height and skeletal growth, Fig. 4 shows the median SDS of height and skeletal age plotted against years post-OLT for both cholestatic (Fig. 4 a,b) and metabolic (Fig. 4 c,d) disease, related to good and poor liver graft function. The plotted height curves for good and poor liver graft function run parallel in the cholestatic disease group (Fig. 4 a), whereas the curves diverge in the metabolic disease group (Fig. 4 c). Therefore, in contrast to the cholestatic disease group, a poorly functioning graft seems to have a negative influence on height growth in the metabolic disease group. The plotted skeletal age curves for good and poor liver graft function diverge, both in the cholestatic and metabolic disease groups (Fig. 4 b,d) indicating that poor liver graft function has an obvious negative influence on skeletal age growth in both diagnostic groups.

Finally, as for the influence of the immunosuppressive regimen on growth, Fig. 5 shows the median SDS of height and skeletal age plotted against years post-OLT in the cholestatic disease group with good liver graft function in relation to the two immunosuppressive regimens used. All children following both regimens were on alternate day maintenance doses of 0.5 and 0.3 mg/kg per day 6 months after transplantation. The median SDS height curves, related to both immunosuppressive regimens (Fig. 5 a), run parallel, indicating no influence of the immunosuppressive regimen on height 2 years after successful OLT in cholestatic disease, whereas the median SDS skeletal age curves, related to both immunosuppressive regimens (Fig. 5 b), converge, indicating that the first regimen has a negative influence on skeletal growth.



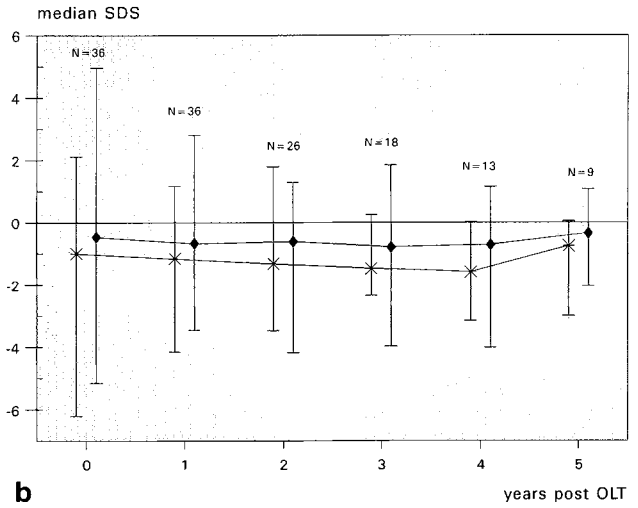
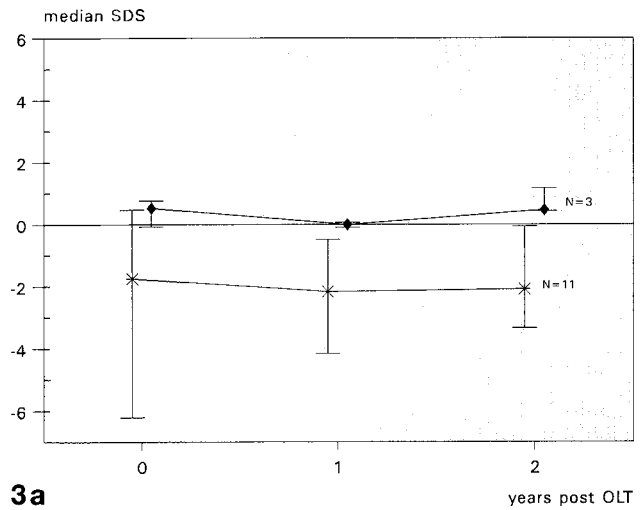


Fig. 2a, b Height (*) and skeletal age (◆) of pediatric transplant recipients: **a** total group of children ($n = 45$); **b** subgroup of children less than 6 years of age at the time of transplantation ($n = 36$) (*SDS*, standard deviation score)



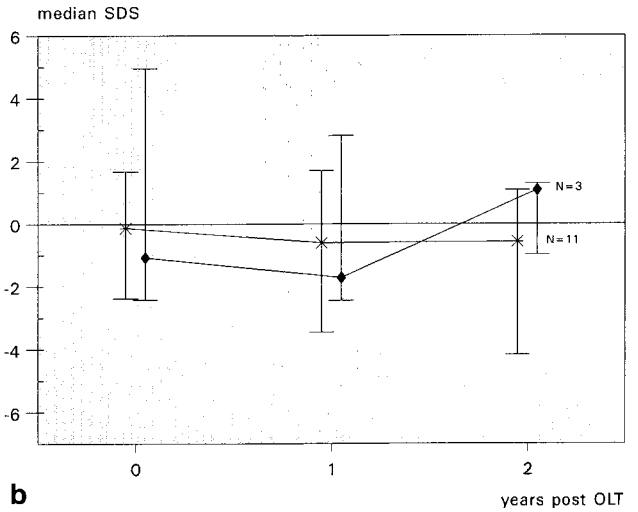


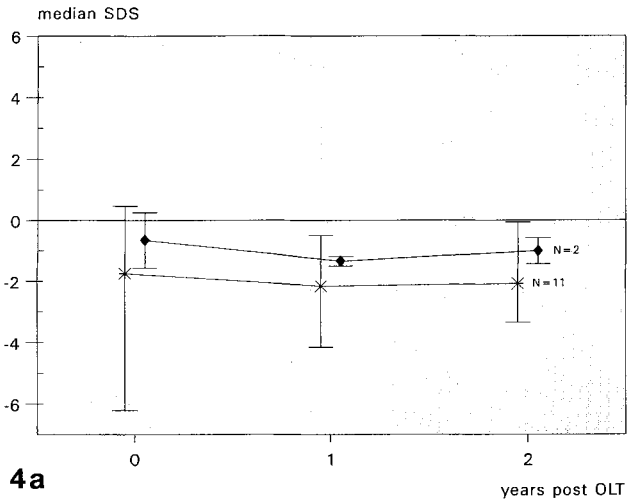
Fig. 3a, b Effect of cholestatic disease (*) and metabolic disease (◆) in recipients with good liver function (minimum follow-up 2 years) on: **a** height; **b** skeletal age (*SDS*, standard deviation score)

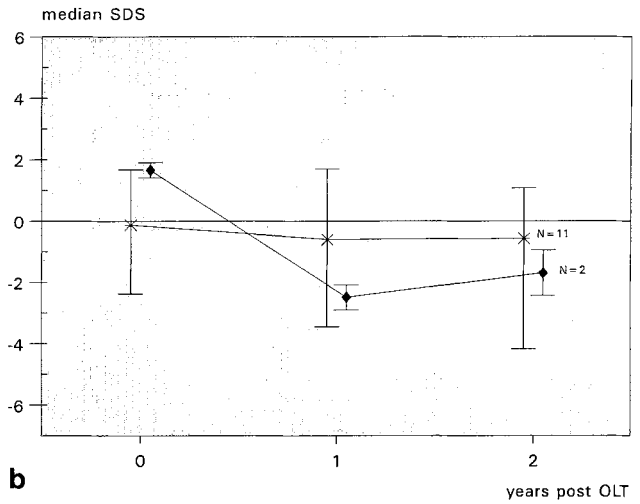
Discussion

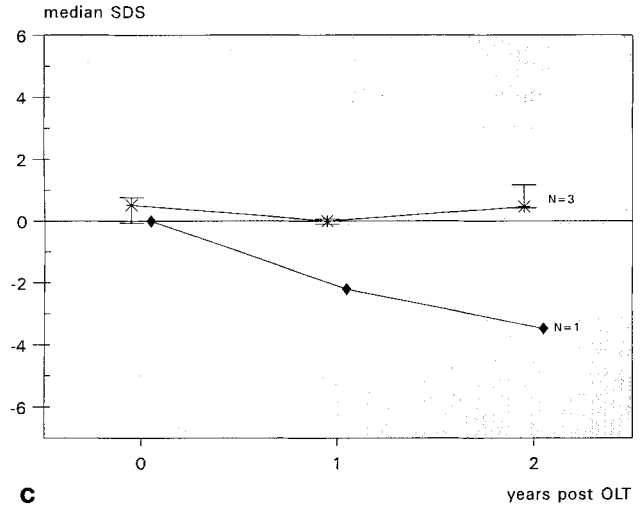
Growth is a prerequisite for good rehabilitation after pediatric OLT, which is why we performed this descriptive, retrospective study on growth in our pediatric transplant population.

Comparing our findings with those from other studies poses problems since inclusion criteria often differ. For example, age distribution of the recipients at the time of transplantation, assessment of graft function, length of follow-up, recipient diagnoses, and immunosuppressive regimens are often different. Furthermore, the concept of catch-up growth is not equally defined in all studies. In order to avoid these problems, we decided to study growth in homogenous groups of pediatric liver transplant patients and in order to explore specific questions concerning growth, some well-defined subgroups were created. Due to the small size of these subgroups, we used descriptive statistics, rather than statistical tests, to present our results; these must, therefore, be interpreted with caution.

Our findings in both the entire group of 45 patients and the subgroup of 36 patients less than 6 years old at the time of transplantation show that there is continuous height and skeletal growth without general catch-up growth over the long term after OLT. Thus, we cannot conclude that catch-up growth is a general phenomenon after OLT. This result is in contrast to the findings







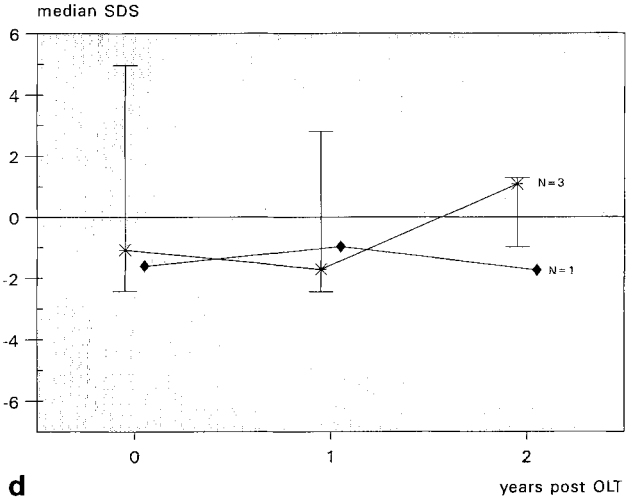
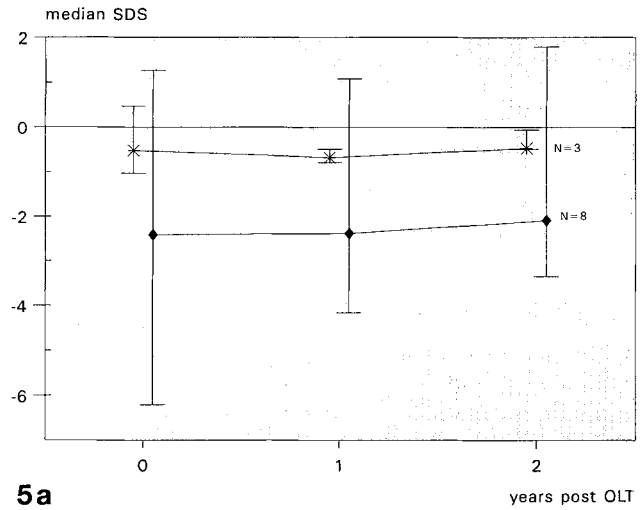


Fig. 4a–d Effect of liver graft function in: **a, b** 13 children with cholestatic disease (minimum follow-up 2 years) and in **c, d** 4 children with metabolic disease (minimum follow-up 2 years) on: **a, c** height and **b, d** skeletal age (* good liver function, ◆ poor liver function, *SDS*, standard deviation score)



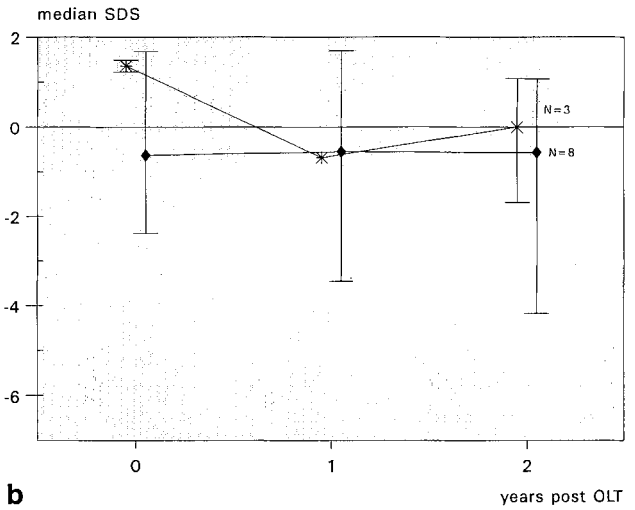


Fig. 5a, b Effect of immunosuppression in 11 children with cholestatic disease and good liver function (minimum follow-up 2 years) on: **a** height; **b** skeletal range (* regimen 1, ◆ regimen 2, *SDS*, standard deviation score)

of Codoner-Franch et al. [6], who demonstrated catch-up growth between 6 months and 2 years after OLT with an increase in the SDS for height of 0.52 at 2 years after OLT. Spolidoro et al. [24], Gartner et al. [9], and Urbach et al. [29] also found catch-up growth in their material. More recent studies with cyclosporin A monotherapy or after withdrawal of steroids have also shown growth improvement or catch-up growth [1, 2, 7]. These contrary findings can be explained by the different study designs and different definitions of catch-up growth.

Our study did not reveal any influence of primary diagnosis on growth in terms of height 2 years after transplantation with proven good graft function. There is a remarkable difference in the level of the plotted median SDS height curves in favor of the group with a metabolic disease (Fig. 3a). Apparently, there is a lack of growth at the time of transplantation in children with a cholestatic disease in contrast to children with a metabolic disease. An explanation for this difference is the earlier onset of cholestatic liver disease and the often more complicated course due to recurrent cholangitis. In contrast, children with a metabolic disease often have a smoother course with a normal synthetic liver capacity.Interestingly, even in the presence of proven good graft function and an alternate day steroid immunotherapy, we did not observe catch-up growth in this selected group of younger children with a cholestatic disease who showed an obvious lack of growth. This finding leads us to postulate that, especially in younger children, a lack of pretransplant growth will not be restored by a general catch-up growth. The study by Codoner-Franch et al. [6] supports our finding of a marked lack of growth before OLT in children with a cholestatic disease and the influence of age at the time of OLT. In contrast to our observations are the findings of general catch-up growth in the case of pretransplant lack of growth in cholestatic disease between 6 months and 1 year after successful transplantation [4, 22].

As for skeletal growth (Fig. 3b), we were able to demonstrate catch-up growth only in the metabolic disease group, i.e., an accelerated bone maturation and junction of the epiphyseal plates.

The influence of liver graft function on height and skeletal growth was explored both in the cholestatic and in the metabolic disease groups. In contrast to the cholestatic disease group, poor graft function negatively influenced height growth in the metabolic disease group (Fig. 4a,c). Children with a metabolic disease generally have a better starting point at the time of OLT than children with a cholestatic disease. Thus, the impact of a poorly functioning graft on height will be detected more easily in the metabolic disease group. In the presence of good graft function, there is a linear increase in height in both diagnostic groups.

As for skeletal growth (Fig. 4b,d), we observed a possible negative influence of poor graft function in the cholestatic disease group and a possible positive influence of good graft function in the metabolic disease group. We have no explanation for the differences in skeletal growth in the two diagnostic groups in the presence of a well functioning liver graft. Of course, these findings have to be interpreted with caution because of the small numbers in these particular subgroups.

The influence of the immunosuppressive regimen was explored in the cholestatic disease group in children with good graft function at successive years after OLT. There was no difference in height growth in children treated with azathioprine, cyclosporin A, and alternate day prednisolone (0.3 mg/kg per day) and children treated with azathioprine and alternate day prednisolone (0.5 mg/kg per day) alone (Fig. 5a). The alternate day steroid treatment, i.e., lower steroid dose, seems to be an important factor for height growth. This is supported by several liver and kidney transplant studies [4, 6, 11, 14, 15, 20, 23]. However, there was a negative influence on the skeletal growth in the azathioprine and alternate day prednisolone alone treatment group (Fig. 5). This is an inconsistent finding, indicating delayed bone maturation despite the higher total prednisolone dose in regimen 1. On the other hand, a delayed junction of the epiphyseal plates permits a postponed and prolonged puberal growth spurt. In children undergoing transplantation at less than 2 years of age, the impact of the steroid treatment on growth is more severe and leads to a lack of height growth [6]. It is still unknown whether these children, transplanted at a younger age, will benefit from a delayed epiphyseal plate junction in the long term, i.e., whether they will show prolonged height growth so that they can reach their expected height.

In conclusion, there is continuous linear growth in both height and skeletal age after OLT without a general catch-up phenomenon in the long term. The primary diagnosis (cholestatic versus metabolic disease) has no influence on height growth 2 years after successful transplantation, whereas there is a positive influence on skeletal growth in the metabolic disease group. Poor liver graft function generally has a negative effect on both height and skeletal growth. The higher prednisolone maintenance dose (0.5 mg/kg per day) in regimen 1 has no negative effect on height growth in the cholestatic disease group, whereas there is a negative effect on skeletal growth. Moreover, our findings indicate that a lack of pretransplant growth will not be restored by general catch-up growth. Therefore, failure to grow has to be avoided or restored by aggressive nutritional management. A nutrition-resistant lack of growth is, in our opinion, an indication for transplantation in an early phase of end-stage liver disease, especially in young children.

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