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Original Article

Evaluation of growth after liver transplantation in a group of Turkish pediatric patients

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Abstract

Aim: Growth failure is considered as an important predictor of negative outcomes after liver transplantation (LT). In our study we aimed to evaluate the growth of liver transplanted children both at the time of LT and on follow-up and to determine factors which are effective on growth.

Materials and Methods: Seventy nine children were included in the study. Evaluation of growth just before the LT and post-LT 6th month,1st,2nd and 3rd years was done by using weight for age Z (WAZ) and height for age Z scores (HAZ).

Results: Sixteen (20.3%) patients had HAZ score<-2 SD (standard deviation) and 13 (16.5%) had WAZ score <-2 SD. Stunting was detected in 17.8% and 23.5% of children with acute liver failure and chronic liver disease, underweight was present in 8.9% and26.5%of them, respectively (p=0.52 and p=0.037, respectively). Both HAZ and WAZ scores increased after LT, especially in the first year. Not mean pre-LT WAZ but mean HAZ score was lower in children who died on follow-up (p=0.023).

Conclusion: Malnutrition before LT is a common problem in children. As stunting is a factor that reduces the chance of survival after LT, prevention and correction is very important.

Keywords: Children; growth; liver transplantation; acute liver failure; chronic liver failure

INTRODUCTION

Growth retardation, which is an additional burden in terms of morbidity and mortality, is a well-known complication of chronic liver disease (CLD) in children (1,2). The reasons include, anorexia, nausea- and vomiting related with inadequate nutrition, cholestasis and portal enteropathy related with inadequate absorption, and failure to supply energy requirements (3-7). Growth retardation in cholestatical liver disease may be due to the malabsorption of fat and fat soluble vitamins and declined protein synthesis (8,9). The liver is the central of the growth hormone (GH)/ insulin-like growth factor-1 (IGF-1) axis, and liver cirrhosis accompanied by GH resistance leads to the impairment of protein, lipid, and carbohydrate metabolisms (3,10,11).

In end-stage liver disease liver transplantation (LT) is the first line therapy which is a well-established, life-saving modality for children. As both pre and post LT under nutrition or growth failure are considered as important predictors of negative outcomes, evaluation of growth as a part of childhood LT follow-up is of paramount importance.

Although there are some data on the growth of children with CLD at the time of LT and on follow-up (1,8), no specific and sufficient data exist about the growth of those who had LT for acute liver failure (ALF). This is partly because most of the published LT series predominantly included children with end-stage liver disease. In our study we aimed to evaluate the growth of children who underwent LT for either ALF or CLD both at the time of LT and on follow-up.

MATERIALS and METHODS

This study is conducted on 79 children who underwent LT at Inonu University Liver Transplantation Institute between May 2009 and May 2020. Demographic and disease related data were noted and evaluated retrospectively. Patients who regularly followed-up after liver transplantation were included in the study, whereas foreign nationals and patients who did not come for regular follow-up were excluded from the study. Approval was obtained from

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the Clinical Research Ethics Committee with the number 2020/889

Evaluation of growth was performed by using the weight for age (WAZ) and height for age (HAZ) Z scores, just before the LT (n=79) and 6 months (n=79), 1 year (n=54), 2 years (n=32), and 3 years (n=10) after the transplantation (standard deviation score; SDS). Anthropometric data was obtained from the hospital records. HAZ and WAZ scores were calculated using the growth charts created by Neyzi et al. for Turkish children with the following formula:

Z score = (x-m) / S

x represents height or weight of the patient, m represents average height or weight appropriate to age and S represents age appropriate height or weight SD. (12).

In this study, depending on the Pediatric End-Stage Liver Disease Model (PELD) scoring system, a height or weight more than 2 SDS below age-appropriate mean is considered to be "growth retardation" and HAZ and WAZ values below -2 were referred as stunting and underweight, respectively.

In clinical practice, intravenous methylprednisolone therapy was initiated during surgery at a dosage of 2 mg/kg/day. Steroid dosage was subsequently tapered to reach 1 mg/kg/day at 4th week post LT and with a progressive switch to an alternate-day therapy at 3rd month and subsequent withdrawal. Cyclosporine A dosages were adjusted to maintain serum levels between 250 and 350 ng/dl for the first 6 months, 100–250 ng/dl for the second 6 months, and 50–100 ng/dl after the first year, respectively. Tacrolimus dosages were adjusted to maintain blood levels between 10 and 15 ng/dl for the first month, and 10 and 5 ng/dl subsequently. Biopsy-proven acute rejection episodes were managed with intravenous methylprednisolone (10 mg/kg per day) followed by a 3-day tapering regimen.

Potential factors that might affect growth, including as gender and age at LT (whether younger or older than 2 years of age), as well as primary diagnosis, graft type, immunosuppression modality, and postoperative complications were analyzed.

Statistical analysis

The data were analyzed by using SPSS for Windows Version 17.0. For the descriptive analyses chi-square, Fisher's exact test, and Mann Whitney U tests were use. A value of p<0.05 was considered as statistically significant.

RESULTS

Mean age was 7.0±5.0 years (6 months-17 years) and 33 (41.8%) children were females and 46 (58.2%) were males. In 47 children (59.5%), living-donor liver transplantation (LDLT) was performed and deceased donor LT (DDLT) was performed in the remaining 32 (40.5%). Thirty-four (43%) procedures were elective surgeries for CLD and 45 (57%) procedures were emergency surgeries for ALF. Of 34 children who had elective surgery, 14 (41.2%) had chronic cholestatical liver disease and 20 (58.8%) had noncholestatical disease. LDLT was performed in 64.4% of patients with ALF whereas in 52.9% of patients with CLD (p=0.3). Mean duration of hospitalization was 37.7 days (11-95).

Mean pre-LT Child-Pugh score of children with CLD were 9.1±2.2.

Patients' HAZ and WAZ scores at the time of LT were -1±1.4 (-6.8 to 2) and -0.75±1.15 (-3.18 to 3), respectively. Sixteen (20.3%) patients had HAZ score <-2 SD, and 13 (16.5%) had WAZ score <-2 SD. While stunting was detected in 17.8 % and 23.5 % of children with ALF and CLD, underweight was present in 8.9 % and 26.5 % of them, respectively (p=0.52 and p=0.037, respectively).

We found that the mean WAZ score of the patients younger than 2 years of age was lower than those of the patients older than 2 years of age (1.3 ± 0.9 vs. -0.5 ± 1.1, p=0.006). The WAZ scores of the patients with cholestatical liver disease were lower in comparison to the noncholestatical patients (-1.5±1.1 vs. -0.5±1.3, p=0.02) (Table 1). No correlation was determined between Child-Pugh score and either HAZ or WAZ scores at the time of LT (p=0.67). Stunting (HAZ<-2) and underweight (WAZ <-2) prevalence according to gender and presentation and according to the specific diagnosis was shown in Table 2 and Table 3, respectively.

Table 1. Mean Pre-LT WAZ and HAZ Values of Children According to Their Sex, Age, and Clinical Presentation

Mean	Girls (N=33)	Boys (N=46)	p
WAZ	-0.63±1.2	-0.8±1	0.45
HAZ	-0.93±1.4	-1±1.5	0.7
	<2 years (N=19)	>2 years (N=60)	p
WAZ	-1.3±0.98	-0.5±1.1	0.006
HAZ	1.4-0.9±	-1±1.5	0.7
	ALF (N=45)	CLD (N=34)	p
WAZ	-0.6±0.9	-0.92±1.3	0.2
HAZ	-0.9±1.24	-1.1±1.7	0.4
	Cholestatic (N=14)	Noncholestatic (N=20)	P
WAZ	-1.5±1.1	-0.5±1.3	0.02
HAZ	-1.6±1.9	-0.8±1.5	0.2
	Metabolic (N=7)	Nonmetabolic (N=27)	P
WAZ	-1.9±1.3	-0.7±1.1	0.3
HAZ	-0.54±1.3	-1±1.4	0.4

WAZ: Weight for age Z scores, HAZ: Height for age Z scores

Table 2. Stunting and Underweight in Children with Different Demographic Features and Presentations

Mean	Girls (N=33)	Boys (N=46)	p
Stunting	5 (15.2%)	11 (23.9%)	0.33
Underweight	7 (21.2%)	6 (13%)	0.33
	<2 years (N=19)	>2 years (N=60)	p
Stunting	3 (15.8%)	13 (21.7%)	0.57
Underweight	6 (31.6%)	7 (11.7%)	0.04
	ALF (N=45)	CLD (N=34)	p
Stunting	8 (17.8%)	8 (23.5%)	0.52
Underweight	4 (8.9%)	9 (26.5%)	0.037
	Cholestatic (N=14)	Noncholestatic (N=20)	p
Stunting	4 (28.6%)	4 (20%)	0.56
Underweight	6 (42.9%)	3 (15%)	0.07
	Metabolic (N=7)	Nonmetabolic (N=27)	p
Stunting	1 (16.7%)	15 (20.5%)	0.8
Underweight	1 (16.7%)	12 (16.7%)	0.98

WAZ: Weight for age Z scores, HAZ: Height for age Z scores

Table 3. Pre-LT Growth According to the Specific Etiology

Fulminant (N=45)	Girls (N=33)	Boys (N=46)
Biliary Atresia(N=9)	8 (17.8%)	4 (8.9%)
PFIC (N=3)	2 (22%)	1 (11%)
Neonatal Hepatitis (N=1)	3(100%)	2 (66.6%)
Wilson (N=7)	1 (100%)	0
Autoimmune hepatitis (N=3)	1 (16.7%)	1 (16.7%)
Budd-Chiari (N=1)	1 (1.26%)	0

PFIC: Progressive familial intrahepatic cholestasis

At 6th month, 1st, 2nd, and 3rd years, WAZ and HAZ scores were -0.5±1.0, -0.5±0.9, -0.2±0.9, 0.09±0.8 and -0.9±1.4, -0.96±1.5, -0.7±1.2, and -0.6±0.9, respectively. Both HAZ and WAZ scores increased dramatically in the first year after LT and subsequently continued to rise gradually (Figure 1).

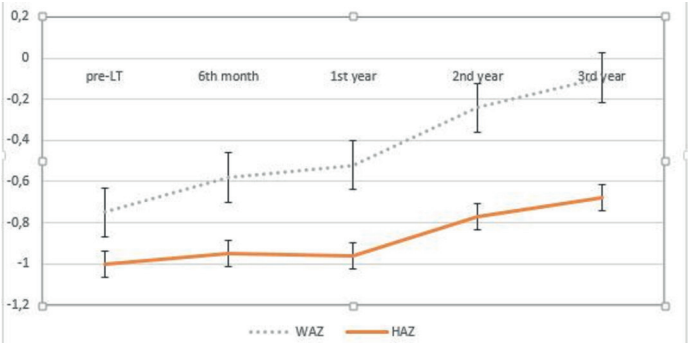

Figure 1. Height and Weight Z scores of children during follow-up

The difference that was observed between the pre-LT HAZ scores of children younger and older than 2 years of age was no longer detected in any post-LT visit. Not statistically but WAZ scores of younger children at post-LT 6th month were lower and 1st year and following WAZ scores were higher compared to those of older children, only 2nd year being statistically significant (p=0.02).

Post-LT WAZ and HAZ scores of the patients in any visit were not different between ALF and CLD. WAZ and HAZ scores of the patient on follow-up in those with or without cholestasis at the beginning were not different, either.

WAZ and HAZ scores on follow-up in respect with age, cholestasis, metabolic disease, ALF and CLD were shown in Figure 2A, B, C and D, respectively.

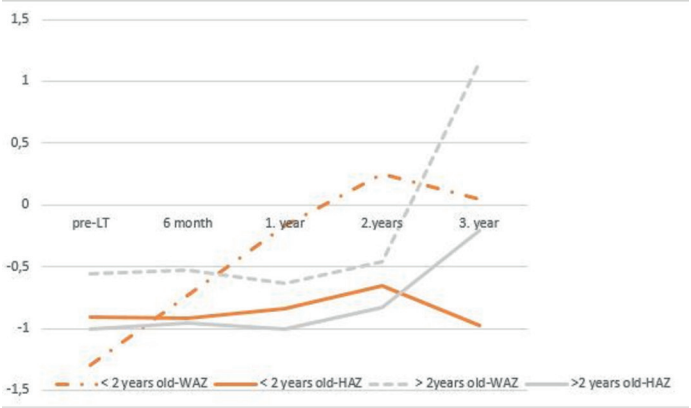

Figure 2A. Height and Weight Z scores of children during follow-up: younger or older than two years of age at the time of liver transplantation

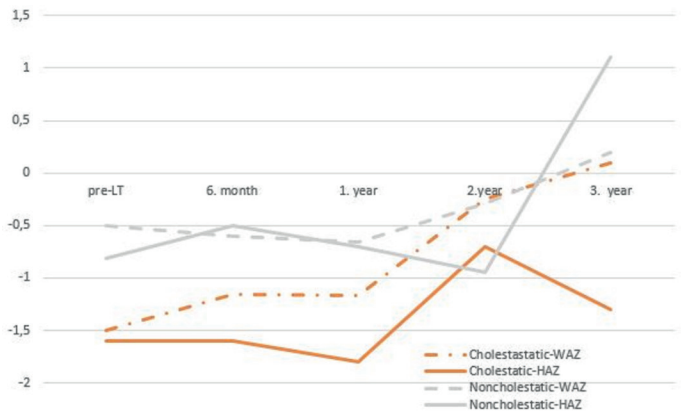

Figure 2B. Height and Weight Z scores of children during follow-up: cholestatic and noncholestatic cases at the time of liver transplantation

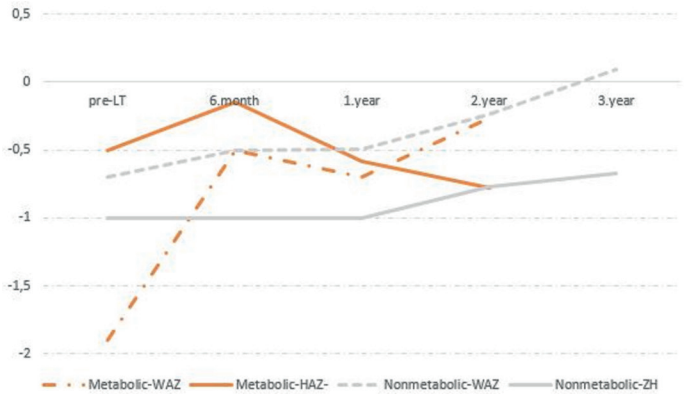

Figure 2C. Height and Weight Z scores of children during follow-up: metabolic or nonmetabolic causes.

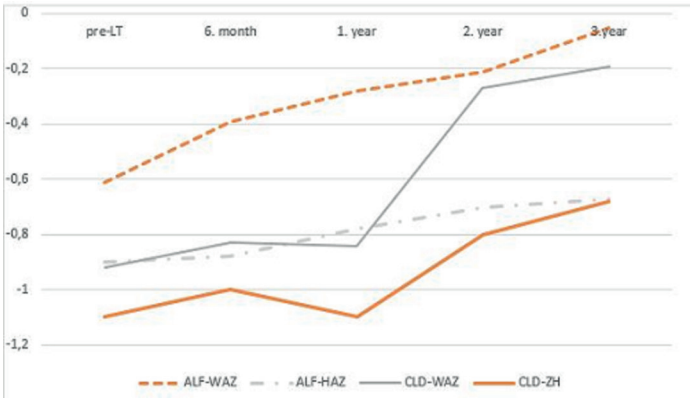

Figure 2D. Height and Weight Z scores during follow-up: children transplanted for acute liver failure or chronic liver disease

Duration of hospitalization did not influence the WAZ or HAZ scores of children at 6th months, 1st, 2nd, and 3rd years (p>0.05). Pre-LT WAZ scores were not different between those who survived or died on follow up, however, mean pre-LT HAZ was lower in those who died on follow-up (p=0.023). Drug choice, cyclosporine or tacrolimus did not influence the WAZ scores of children at any of the visits. Acute rejection occurred in five patients. Mean WAZ score was not affected with rejection episodes on follow-up (p>0.05) but mean HAZ score was lower at 6th month who had a rejection episode (p=0.01).

DISCUSSION

In this study, which evaluated growth in children who underwent LT, we found that 20.3% and 16.5% of the patients had stunting (height for age Z score<-2) and underweight (weight for age Z score<-2) before LT. A previous study reported growth retardation in one-third of the children (34.7%) (8). While mean height for age Z score was -1 in our study at the time of transplantation it was reported as -1.5 by Alonso et al. (13), 1.9 by Bartosh et al. (14), -1.15 by Codoner-Franch et al. (14), -2.21 by Mc Diarmid et al. (16). Short stature is a sign of chronic disease so the higher Z score in our study compared to other studies might be attributed to the fact that almost half of our cases had ALF. It might also be relevant for the lower underweight rate. Despite better mean Z score values, it was interesting to find a still high rate of acute and chronic malnutrition in our fulminant cases. This finding was thought to be due to the fact that some of the ALF cases might have an unknown underlying chronic disease and also to the relatively high rate of stunted growth in our country. According to the national health survey data, 9.5% of children under five years of age have stunted growth (17).

In our study, the WAZ score of younger children was lower than that of older ones. In the first two years of life, diseases have a more significant impact on nutritional status because the nutritional requirements are higher and growth is faster. Our observation that WAZ of children < 2 years had a faster increase after LT (Figure 2A) supported that knowledge. The effect of the age at LT on growth had been reported in many studies before (3,8,16,18,19). Another finding was the worse growth in cholestatical children compared to non-cholestatical ones. From that point of view, more severe growth failure in children younger than two years of age can be related to higher rate of cholestatical patients in this group and to higher rate of ALF in older children. Alonso and colleagues [13] reported that failure to thrive was more significant in children who required LT in younger ages and in children with cholestatical liver disease. They also have shown that the most important factor that determines post LT growth is the age at transplantation in children with biliary atresia. Children under two years of age grow faster than children above two because hormonal changes return to normal after one to two months after transplantation and younger children have a greater growth potential.

In our study, we found that both HAZ and WAZ scores increase progressively after LT and children under the age of two years caught up growth at the third year. At the post-LT third year, 100% of our patients had weight for age and height for age Z scores >-2. Baran and colleagues3 reported that their cases reached target height at the third year, and 90% of them had a Z score >-2 at the fifth year. Park et al. (18) reported that the patients grew fast in the first two years after LT, and all of them reached target height at the seventh year. However, Scheenstra et al. (19) reported that although children grew well in first two years after LT, they did not reach target height during follow-up. On the contrary, Viner et al. (20) revealed that catch up growth started after the second year and continued until the seven years of age. As Figure 1 shows, while weight for age Z score had a continuous increase in our series, height for age Z score increased minimally in the first six months, stayed constant between six months and the first year, and significantly increased after the first year. The increase after the first year can partly be attributed to the effects of steroid withdrawal.

Similar to that of Baran et al. (3), our study showed that gender, disease severity, etiology (ALF or CLD), duration of hospitalization, type of immune suppression did not have any effect on growth after transplantation. Baran et al. (3) reported that the type of transplantation had no effect on growth after LT but we showed that our recipients with a living donor had better WAZ and HAZ scores at the time of transplantation and during follow-up. We attribute this to the fact that in the living donor group most of the recipients had ALF which means they were mostly without growth failure. They might also have received better care from their parents. Similarly, Park et al. (18) found that target height was always reached in follow-up after LT from a living donor. They related this to the better nutritional status of their patients with living donors. Renz et al., in their short-term study reported that recipients with a living donor had a better HAZ score at the time of transplantation and 1 year afterwards (21).

In our study, the preoperative WAZ was similar between children who survived and those who did not, but the preoperative mean HAZ was significantly lower for the

children who did not survive (p=0.023). Barshes and colleagues (1) reported that recipient height at the time of transplantation was the best indicator of malnutrition and a height for age Z score below -1.5 was related to longer hospitalization and intensive care unit stay. In two separate studies with 83 and 956 patients, respectively, Bucuvalas et al. (22,23) reported that low height for age Z scores before transplantation was related to the duration of hospitalization.

Lack of skinfold thickness or mid arm circumference data is one of the limitations of the study as WAZ is not an ideal indicator of underweight in children with liver disease due to probable ascites, edema and/or organomegaly. The other is the low number of the cases who were evaluated in the 3rd year, which might affect the statistical significance of some parameters.

CONCLUSION

Malnutrition is common in pediatric patients before LT, especially in those younger than 2 years. Stunted height, in particular, decreases post transplantation survival thus the prevention and correction of malnutrition before LT is of paramount importance. AS growth potential is higher in the first two years of life, LT as soon as possible after a diagnosis of end-stage liver disease is crucial for a rapid catch-up growth.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Approval was obtained from the Inonu Universty Clinical Research Ethics Committee with the number 2020/889.

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