Long-Term Linear Growth and Puberty in Pediatric Liver Transplant Recipients

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Objective To explore linear growth, puberty, and predictors of linear growth impairment among pubertal liver transplant recipients.

Study design Review of data collected prospectively through the Studies of Pediatric Liver Transplantation registry. Thirty-one variables were tested as risk factors for linear growth impairment, and factors significant at $P < .1$ were included in a logistic regression model. Risk factor analysis was limited to 512 patients who had complete demographic and medical data.

Results A total of 892 patients surviving their first liver transplant by >1 year, with ≥1 height recorded, who were between 8 and 18 years old between the years 2005 and 2009 were included. Median follow-up was 70.2 ± 38.6 months, mean age was 12.9 ± 3.3 years, and mean height z-score (zH) was −0.5 ± 1.4 SD. Twenty percent had linear growth impairment at last follow-up. Of 353 subjects with Tanner stage data, 39% of girls and 42% of boys ages 16-18 years were not yet Tanner 5. Growth impairment rates were higher among boys than girls (30% vs 7%, $P < .05$) at Tanner stage 4, and occurred in 8/72 (11%) of Tanner 5 subjects. Among patients with parental height data, zH were lower than calculated mid-parental zH ($P < .005$). Independent predictors of growth impairment included linear growth impairment at transplant (OR 11.53, $P \leq .0001$), re-transplantation (OR 4.37, $P = .001$), non-white race ($P = .0026$), and primary diagnosis other than biliary atresia ($P = .0105$).

Conclusions Linear growth impairment and delayed puberty are common in pubertal liver transplant recipients, with pre-transplant growth impairment identified as a potentially modifiable risk factor. Catch-up growth by the end of puberty may be incomplete. *(J Pediatr 2013;163:1354-60)*.

Physical growth is an important indicator of overall health in children with chronic disease states, including those with liver disease who require transplantation. Prior to transplant, factors that contribute to linear growth impairment include increased resting energy expenditure, decreased intake, nutrient malabsorption, abnormal nitrogen balance, and alterations of the growth hormone axis.[1-3] Linear growth is expected to improve after replacement of a diseased liver as growth hormone and insulin-like growth factor 1 levels return to normal and nutritional status improves.[4] The beneficial effects of restored hepatic function, however, may be offset by immunosuppressive medication, particularly high dose glucocorticoids.[5,6] Previous studies have demonstrated that catch-up growth following transplant occurs but may be incomplete, and puberty is often delayed.[7,8]

In an analysis of prepubertal children after liver transplant (n = 1143), risk factors for poor linear growth were identified as prolonged steroid exposure, lower weight percentiles at time of transplant, linear growth impairment prior to transplant, and metabolic disease as the primary diagnoses.[9] Analyses of factors impacting linear growth after transplant in the pubertal age group are limited by relatively small sample sizes and a wide distribution of age at transplant, primary disease, and outcome status. The aims of this study were to describe the linear growth and pubertal trends of older children included in the Studies of Pediatric Liver Transplantation (SPLIT) registry and identify potentially modifiable predictors of linear growth impairment in this large, prospective, multi-center cohort.

Methods

Initiated in 1995, the SPLIT registry is a multi-center data repository for pediatric liver transplant candidates and recipients and has included 44 centers in Canada and the US. All SPLIT centers have individual institutional review board

GGTP	Gamma glutamyltranspeptidase
MPH	Mid-parental height targets
rhGH	Recombinant human growth hormone
SPLIT	Studies of Pediatric Liver Transplantation
zH	Height z-score

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*A list of members of the SPLIT Research Consortium is available at www.jpeds.com (Appendix).

The authors declare no conflicts of interest.

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approval, and individual informed consent is obtained from the parents or guardians prior to patient enrollment. Coded information is submitted to the SPLIT data coordinating center via a standardized Web-based data entry system beginning at the time of listing for transplantation. Data collection includes detailed information regarding clinical status, laboratory values, medical and operative therapies, and patient complications and outcomes.

The patient sample used in this analysis included children with data entered in the registry between ages 8 and 18 years who had undergone first liver transplantation while included in the registry, survived at least 1 year post-transplant, and had at least 1 recorded height between August 1, 2005 and May 31, 2009. The lower age limit of 8 years was selected to improve capture of all subjects who might undergo puberty in the study period. We chose August 2005 as the start date because that marked the introduction of Tanner staging as an element of SPLIT data collection.

Data Collection and Analysis

Linear growth data were obtained by wall-mounted stadiometer for ambulatory children. Heights were measured prior to transplant, at time of transplant, at 6, 12, 18, and 24 months following transplant, and annually thereafter. Some patients may have had multiple measurements over sequential years included if they continued to meet inclusion criteria (range 1-4 measurements per subject). Parental heights were self-reported for the majority of patients for whom data were collected, with 3 centers contributing 82% of the results. Height SD scores (height z-score [zH]) for patients and mid-parental height targets (MPH) were calculated using age- and sex-specific references for the general population provided by the Centers for Disease Control and Prevention growth charts.[10] Seven patients received recombinant human growth hormone (rhGH) therapy and were excluded from the study. Tanner stage (pubic hair for boys and breast development for girls) was assessed by the attending gastroenterologist during the course of the physical examination for 63% of patients and by self-report for the remainder, using a validated self-report form.[11,12] For the purpose of this analysis, linear growth impairment was defined as a zH below −1.64 (5th percentile for age and sex). Factors analyzed as possible predictors of linear growth impairment included 5 demographic and 26 medical variables routinely collected by SPLIT (**Table I**; available at www.jpeds.com). These were hypothesized to either have a direct impact on linear growth or to be markers for acuity of illness at the time of transplant.

Statistical Analyses

Data were summarized using means and SE for continuous factors and proportions for categorical factors. Risk factors for linear growth impairment were identified using logistic regression. Univariate analyses were performed using Kruskal–Wallis test for continuous factors and χ^2 test for categorical factors on 31 variables (**Table I**). Factors significant at the 0.10 level in the univariate analyses were included in the multivariate model, which was derived using stepwise backward elimination procedure. Model simplification continued until the reduced model yielded a significant worsening of fit according to the likelihood ratio criterion ($P \leq .05$). All statistical analyses were performed using SAS for Windows, v. 9.1 (SAS Institute Inc, Cary, North Carolina).

Results

A total of 1022 children underwent primary liver transplant during the study period and 892 met the inclusion criteria. The mean age at transplant was 7.0 ± 5.1 years, the mean age at survey was 12.9 ± 3.3 years, and mean zH was −0.5 ± 1.4 SD. The mean follow-up for all subjects was 70.2 ± 38.6 months; 43% of patients were transplanted between ages 5 and 12 and 15.8% were transplanted as infants. A complete list of patient demographic and clinical status is displayed in **Table II** (available at www.jpeds.com).

Linear growth impairment defined as a height less than the 5th percentile at last follow-up was observed in 174 children (19.5%). **Figure 1**, A displays the percentage of subjects

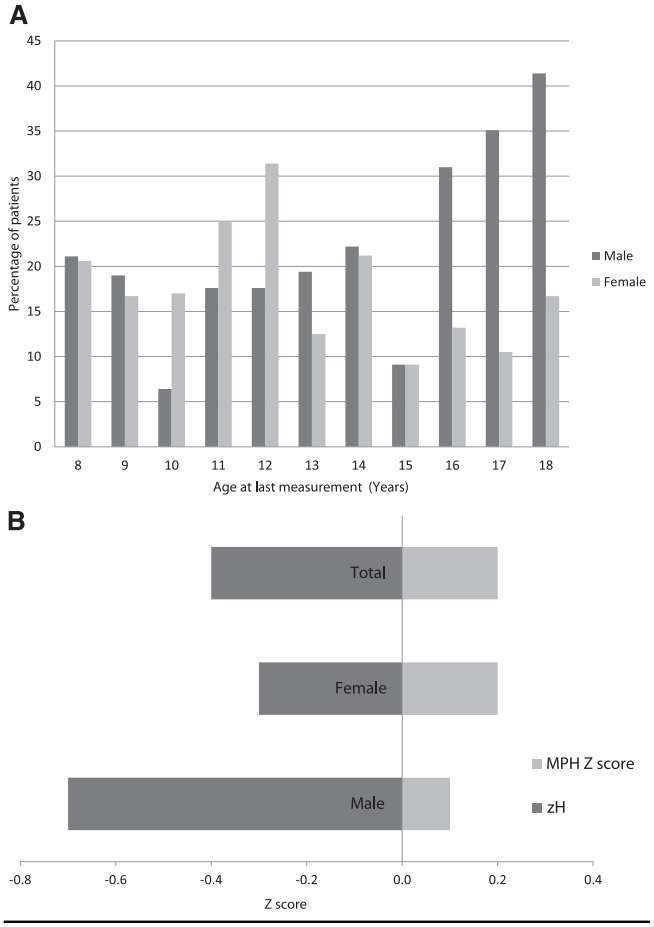

Figure 1. Prevalence of linear growth impairment at last follow up visit. **A,** By age compared with the general population (n = 892). The percentage of males is greater than females in the late teens. **B,** By mean zH compared with calculated mean MPH zH (n = 138). $P < .005$ for the 3 groups.