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Longitudinal Study of Cognitive and Academic Outcomes after Pediatric Liver Transplantation

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Abstract

Objective—To determine the evolution of cognitive and academic deficits and risk factors in children after liver transplantation.

Study design—Patients 2 years after liver transplantation were recruited through Studies of Pediatric Liver Transplantation. Participants age 5–6 years at Time 1 completed the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition, Wide Range Achievement Test, 4th edition, and Behavior Rating Inventory of Executive Function (BRIEF). Participants were retested at age 7–9 years, Time 2 (T2), by use of the Wechsler Intelligence Scales for Children, 4th edition, Wide Range Achievement Test, 4th edition, and BRIEF. Medical and demographic variables significant at $P = .10$ in univariate analysis were fitted to repeated measures modeling predicting Full Scale IQ (FSIQ).

Results—Of 144 patients tested at time 1, 93 (65%) completed T2; returning patients did not differ on medical or demographic variables. At T2, more participants than expected had below-average FSIQ, Verbal Comprehension, Working Memory, and Math Computation, as well as increased executive deficits on teacher BRIEF. Processing Speed approached significance. At T2, 29% (14% expected) had FSIQ = 71–85, and 7% (2% expected) had FSIQ ≤ 70 ($P = .0001$). A total of 42% received special education. Paired comparisons revealed that, over time, cognitive and math deficits persisted; only reading improved. Modeling identified household status ($P < .002$), parent education ($P < .01$), weight z-score at liver transplantation ($P < .03$), and transfusion volume during liver transplantation ($P < .0001$) as predictors of FSIQ.

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*List of members of SPLIT and FOG is available at www.jpeds.com (Appendix).

The authors declare no conflict of interest.

Conclusions—More young liver transplantation recipients than expected are at increased risk for lasting cognitive and academic deficits. Pretransplant markers of nutritional status and operative complications predicted intellectual outcome.

Children surviving liver transplantation are reported to have a greater probability of intellectual deficits^{1–5} and learning difficulties^{5–7} compared with healthy peers. A few studies have examined cognitive function in children before and after liver transplantation, and typically have found no improvement.^{6,8–10} However, these studies are plagued by methodologic problems, including small, single-center samples, broad age ranges, and retrospective design. Furthermore, the developmental course of cognitive and academic deficits in children after their initial recovery from liver transplantation has not been well established, and thus, it is unknown whether these deficits are static, abate as children mature, or become more prominent over time as with late effects of cancer treatment.¹¹ Early brain injury has the potential for significant, long-lasting cognitive deficits.^{11,12} Several factors have been associated with worse cognitive outcomes after pediatric liver transplantation; yet, previous single-center studies examining the risk in these patients have been limited in scope and reliability.^{3,4,9}

The Functional Outcomes Group (FOG) included 20 pediatric liver transplantation centers in the Studies of Pediatric Liver Transplantation (SPLIT) collaborative that participated in a longitudinal study of 144 pediatric liver transplantation survivors. Participants were 5–6 years of age and at least 2 years beyond liver transplantation at initial testing. This age range was selected to determine whether screening would accurately identify developmental risk around the critical time of school entry and to assess patients with early transplant experience (within the first 4 years of life). Despite average performance overall, pediatric liver transplantation recipients were twice as likely as expected to have an IQ of ≤ 85 and also demonstrated an increased prevalence of deficits in executive function (eg, organizational skills) (EF) working memory, reading, and math compared with the normal population.⁵

These results provided evidence for increased risk of cognitive and academic deficits after liver transplantation in young children compared with the normal population. However, young children's cognitive functioning is more variable and measurement less reliable; test scores do not become stable and reliable predictors of long-term cognitive outcomes until the child is about 7 years of age.¹³ Furthermore, testing at one time point in early childhood was not adequate to determine whether deficits would evolve with maturation in those who demonstrated below-average functioning. Although many participants at initial testing were already well beyond early recovery from liver transplantation (up to 4 years), we were interested in the developmental trajectory of deficits in children with early liver transplantation. An additional study objective was analysis of risk factors for lower cognitive functioning that might form the basis of future intervention studies to prevent or ameliorate cognitive delay.

This report details the results of follow-up evaluation in this patient cohort at age 7–9 and includes an analysis of risk factors associated with lower cognitive function. We postulated cognitive deficits identified at a greater rate than expected at age 5–6 would persist due to

lasting changes in the developing brain. We also hypothesized that several pre-transplantation (eg, nutritional and growth deficits, severity of liver disease), as well as peri- and posttransplantation factors such as complications, ongoing medical disability, and long-term exposure to calcineurin inhibitors would contribute to cognitive outcomes in a dynamic fashion.

Methods

FOG was an independently funded ancillary study of the SPLIT registry. Liver transplantation recipients at participating medical centers were identified and recruited through the infrastructure of the SPLIT registry between June 1, 2005 and December 31, 2009. At recruitment, participants were 5–6 years of age, fluent in English (patient and primary caregiver), and at least 2 years from their most recent liver transplantation. One patient received a second liver transplantation between evaluations but had recovered by 1 year at follow-up. Patients with uncorrected vision or hearing loss and those with serious neurologic injury that would preclude participation in testing were excluded. Because of the increased prevalence of hearing deficits in pediatric liver transplantation recipients,¹⁴ all patients were screened for hearing at the initial visit, and those with uncorrected hearing loss between 500 and 4000 Hz were excluded. Three patients were rescreened before follow-up testing due to ototoxic drug exposure ($n = 2$) and retransplantation ($n = 1$); all 3 patients passed the hearing screen. Additional details regarding methods can be found in the initial report of FOG results.⁵

This study was a longitudinal assessment of cognitive function beginning when the child was 5–6 years of age (time 1; T1) and continuing with follow-up testing 18–36 months later at age 7–9 years (time 2; T2). The study was approved by institutional review boards at participating centers and written informed consent was obtained before participation. Participants were recruited, consented, and tested at the transplant center where they received medical follow-up. Past, as well as present, demographic and medical data for participating patients were extracted from the SPLIT registry database.

Instruments and Testing Procedure

IQ—Patients completed the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III)¹⁵ at T1 and the Wechsler Intelligence Scales for Children, 4th edition (WISC-IV)¹⁶ at T2. The WPPSI-III provides a lower test “floor” to better capture functioning at the lower end. Composite scores were generated for the WPPSI-III/WISC-IV including Full Scale IQ (FSIQ), Verbal IQ/Verbal Comprehension (VC), Performance IQ/Perceptual Reasoning (PR), and Processing Speed (PS), and Working Memory (on WISC-IV) (WM). These standard scores have a mean of 100 and SD of 15 in the normal population. These are psychometrically sound and commonly used instruments that, although structurally somewhat different, are highly correlated (FSIQ, $r = 0.89$; Verbal IQ/VC, $r = 0.83$; Performance IQ/PR, $r = 0.79$; PS, $r = 0.65$).¹⁶

Achievement—At both time points, participants completed the Wide Range Achievement Test, 4th edition (WRAT-4)¹⁷: Word Reading and Math Computation subtests as a screener of basic academic skills. Standard scores are reported with a mean of 100, SD 15.

Executive Function—WM at T2 (WISC-IV) and PS at both time points (WPPSI-III and WISC-IV) provided a screen of these discrete aspects of EF. In addition, at both time points, parents and teachers completed the Behavior Rating Inventory of Executive Function (BRIEF), a survey of executive function tapping real-life situations (eg, “forgets to hand in homework, even when completed”).¹⁸ This measure yields an overall Global Executive Composite (GEC), and 2 summary indices: Metacognition index (MI) and Behavioral Regulation (BRI). MI is composed of Initiate, working memory, Plan/Organize, Organization of Materials, and Monitor subscales, and BRI is composed of Inhibit, Shift, and Emotional Control subscales. This measure yields T scores (mean of 50, SD 10), with greater scores indicating more concerns. The BRIEF was selected to efficiently assess several aspects of executive functioning, an area suspected to be vulnerable in pediatric patients with liver transplantation as it is in patients with other types of brain insult.^{11,12} Although an indirect measure of EF, the BRIEF has excellent reliability and validity, and it is designed to assess EF within the complex environments of the child’s everyday experiences from multiple perspectives.

The BRIEF parent report was completed for all participants at T2, but only 90 participants had reports at both time points. BRIEF teacher reports were completed in 62 of 93 returning patients, but longitudinal comparison was possible in only 36 patients. The 36 patients with teacher reports for both time points did not differ statistically from the 57 patients with one or more missing forms on age at liver transplantation, interval from transplant, primary caregiver’s highest level of education, race, or sex. Reasons for missing forms were: not administered due to summer break (n = 11), forms not returned (n = 19), missing teacher contact information (n = 1), and teacher report not available from T1 (n = 26).

Validity Rating—Examiners at individual centers completed a validity rating form after testing to provide information regarding factors that may have interfered with test administration. Data from cases in which the examiner indicated serious concerns (no more than 6 cases on each measure at T1 and 1 case at T2) were not included in the final analysis. Additional missing IQ and achievement data (1 case at T1) was attributable to examiner error or logistical problems resulting in incomplete test administration. A total of 92 participants had IQ data at T2 and 89 participants had data for comparison across both time points; 93 had WRAT-4 data at T2, and 92 had both time points. One participant had some missing scores within measures because of scores that were so low they were incalculable.

School Functioning—Qualitative information regarding school functioning was obtained through SPLIT via parent completion of the School Attendance and Academic Performance Survey⁷ at medical follow-up visits. Forms were not collected for 15 participants at T2.

Statistical Analyses

Demographic and medical data of patients tested at T1 and T2 were compared with patients tested only at T1 by χ^2 statistics to ensure the groups were similar. WPPSI-III scores (T1) and WISC-IV scores (T2) were pooled in this manuscript for analysis of longitudinal data. Categorical comparisons of IQ, executive, and academic data to the normal population were made using χ^2 test for goodness of fit in order to determine whether, as hypothesized, our

sample reflected an over-representation of lower scores. Variables were categorized by intervals of 1 SD; for WISC-IV and WRAT-4, categories were: 85, 86–100, 101–115, and >115. For BRIEF, categories were >60, 51–60, 41–50, and 40.

The hypothesized stability of cognitive deficits over time was examined via comparison of T1 to T2 scores using paired Student *t* tests. The Type I error rate was maintained at 0.05 by the Hochberg adjustment for multiple comparisons; an adjustment was made separately for each instrument.¹⁹

The contribution of pre-, peri-, and posttransplantation factors to cognitive outcomes was examined by the use of univariate analysis, with visit (T1 or T2) included to identify predictors of FSIQ. Variables chosen for univariate analysis were available through the SPLIT registry, had conceptual and/or empirical support, had less than 25% missing data, and at least 10% of patients in 2 categories (Table I; available at www.jpeds.com). Only variables that were significant at the $P = .1$ level in univariate analysis were considered for multivariate linear and logistic repeated measures regression modeling (15 and 12 factors, respectively). For the linear regression model, an unstructured covariance matrix was used to model the repeated measures within subjects. Backward elimination procedure was performed for both models, removing factors one at a time, least significant first, until all factors were significant at the .05 level. Only subjects with complete data from both testing time points for all selected factors were included in this process. Then, to increase the sample size and confirm results, the multiple regression was re-run on all subjects with complete data for variables in the final model. For the linear model, this increased the sample size to 109 subjects with 45 subjects having complete data at both testing time points, allowing inclusion of 154 records. A logistic regression model was performed using the same process to provide internal consistency for the model. The final logistic regression model included 90 patients, 64 with data from both time points, for a total of 154 records. The SAS software package version 9.2 (SAS Institute Inc, Cary, North Carolina) was used for the analysis. All statistical tests were 2-sided, and $P < .05$ was considered to be significant.

Results

Of the 456 patients in the SPLIT registry who were eligible for enrollment during the study period, 260 were approached for recruitment, and 144 (55% of those approached) participated. Reasons for failure to participate have been previously described, and participants and nonparticipants did not differ on basic demographic or medical variables.⁵ Of the original 144 patients tested at the first time point, 93 (65%) completed testing at T2. Reasons for not returning included patient not eligible during study or no visit in window ($n = 22$), declined because of distance or other reason ($n = 12$), miscellaneous, including scheduling difficulties ($n = 15$) and death or hospitalization (one each). Returning patients did not differ by age at liver transplantation, diagnosis, donor type, or demographics (sex, race, primary insurance, primary caregiver education). Mean age at testing was 6.2 ± 0.6 years at T1 and 8.5 ± 0.7 years at T2 (Table II).

Parent-Reported School Functioning/History

At T2, 42% ($n = 33$) of respondents on the School Attendance and Academic Performance Survey reported their child had received special education (ie, formal, individualized supports provided by a specially trained teacher) within the past 12 months ($n = 21$ speech/language, $n = 24$ reading/language arts, $n = 17$ math, $n = 9$ physical/occupational therapy). Parents also indicated that 14% ($n = 11$) had had a 504 plan (accommodations at school), 10% ($n = 8$) had repeated a grade or been held back, and 14% ($n = 11$) had a previous diagnosis of attention-deficit/hyperactivity disorder. At T2, 68% ($n = 52$) of participants were reported to be in first or second grade, and 32% ($n = 24$) were in third or fourth grade. Of 129 families in the study who answered a question regarding language use in the home, 96% ($n = 124$) reported speaking English only, or at least equally, with a second language at home, and 2% ($n = 3$) spoke primarily a language other than English at home; 2 responses were missing. A total of 5% ($n = 6$) reported that the participant had a hearing impairment requiring hearing aids.

Stability of Functioning over Time

Intellectual Functioning at T2—Intellectual, executive, and academic functioning at T1 were previously reported,⁵ but overall T1 means are provided for comparison with the T2 sample (Table III). At T2, more patients scored below expected levels compared with the normal distribution on goodness of fit analyses for WISC-IV FSIQ ($P = .01$), VC ($P = .003$), and WM ($P = .01$). There was a trend towards lower PS ($P = .08$), but PR was not significantly different from norms (Figure). Furthermore, when categories were collapsed for higher scores (>85) and expanded at the lower end (FSIQ = 71–85; FSIQ < 70), the discrepancy with the normal population is even more significant ($P = .0001$). Twenty-nine percent of T2 participants had FSIQ = 71–85 vs 14% expected, and 7% had FSIQ < 70 vs 2% expected. Paired comparisons did not reveal any significant change over time in FSIQ, VC, PR, or PS.

Academic Skills at T2—Consistent with T1 results, more participants at T2 performed below expected levels on WRAT-4 Math Computation compared with the normal distribution ($P = .001$). However, Word Reading was no longer different from test norms at T2. Paired comparisons revealed no change in Math Computation, but an improvement in Word Reading scores from T1 to T2 ($P = .0001$; Table III). Participants who had received special education before T2 did not differ in terms of the proportion with improved reading and math scores on the WRAT-4 compared with those who did not receive special education.

Executive Function at T2

Parent BRIEF: At T2, there was no difference in the distribution of BRIEF parent composite scores (GEC, BRI, MI) or any subscales in comparison with the normative population. Paired analyses, did not reveal significant differences in mean composite scores between the 2 testing time points (Table III).

Teacher BRIEF: Similar to T1 results, more participants at T2 had worse GEC ($P = .04$), BRI ($P = .01$), and MI ($P = .03$) than expected in comparison with the normative population.

At T2, 25.8% of participants with BRIEF teacher reports had MI scores ≥ 65 (clinically significant range) vs 6.68% expected ($P = .0001$). All subscales were also significantly different from the normal population (Table IV; available at www.jpeds.com). Paired comparisons revealed no changes in composite scores across time (Table III).

Factors Predicting Cognitive Outcomes

Univariate analysis was performed using FSIQ as a continuous dependent variable and independent variables reflecting pre-, peri-, and posttransplantation factors (Table I). Fifteen factors significant at $P \leq .1$ were selected as candidate variables for the initial multivariate linear repeated measures regression model: visit, sex, race, household status, parent education, insurance at liver transplantation, primary disease, hospitalization status at liver transplantation, height z score < -2 SD at liver transplantation, weight z score < -2 SD at liver transplantation, donor type, reoperation in first 30 days, Pediatric End-stage Liver Disease score at liver transplantation, intraoperative transfusion requirement in mL/kg, and hospital days since last follow-up visit. Backward selection identified 5 variables in the final model as depicted in Table V: visit, household status, parental education, weight z score at liver transplantation, and intraoperative transfusion requirement.

Likewise, we performed univariate analysis with the same independent variables to predict FSIQ ≥ 85 (Table I). The following 12 factors were included in the initial multivariate logistic repeated measures regression model: visit, sex, household status, parent education, hospitalization status at liver transplantation, height z score < -2 SD at liver transplantation, weight z score < -2 SD at liver transplantation, donor type, Pediatric End-stage Liver Disease score at liver transplantation, cold ischemia time (hours), intraoperative transfusion requirement in mL/kg, and days hospitalized since last follow-up visit. Backwards selection yielded a final model that mirrors the results of the linear regression model (Table V).

Discussion

We report a prospective multicenter longitudinal evaluation of neurocognitive functioning after pediatric liver transplantation. One other study that examined 2 time points after liver transplantation in children was designed to compare functioning before and after liver transplantation and used a smaller, younger sample ($N = 25$; age 1 year and age 5 years at follow-ups).¹⁰

Similar to T1 results, overall means at T2 were uniformly within the average range on IQ testing; however, significantly more liver transplant recipients than expected had below average functioning on most variables. At follow-up, the distribution of scores on the WISC-IV was significantly shifted downward compared to the normal population for FSIQ, VC, and WM, and there was a trend for PS. As before, more than twice as many as expected at T2 had FSIQ scores ≥ 85 .

A greater proportion of patients than expected demonstrated executive function weaknesses that persisted over time. As seen at T1, teachers reported more significant problems than parents on the BRIEF at follow-up, likely as a result of the different demands in the school setting. Teachers reported increased concerns compared with the normal population across

all areas of executive functioning on the BRIEF. This finding indicates that, at least within the school setting, liver transplantation recipients have a greater prevalence of problems in such areas as the ability to inhibit behaviors; shift/transition when demands or expectations change; regulate mood; get started on tasks; use working memory; plan and organize time, tasks, and materials; and use self-monitoring strategies. Working memory (mental juggling/holding information in mind briefly for “online processing”) was implicated as an important concern in greater than expected numbers on both the WISC-IV and on the BRIEF. Of note, on the teacher BRIEF more than 3 times as many patients as expected had clinically significant deficits in the metacognitive executive domain.

Not surprisingly, attention deficits are also implicated in this population. At T2, 14% were identified by parent report as having received a diagnosis of attention deficit/hyperactivity disorder. Although attention and executive problems are common complaints in patients with hepatic encephalopathy,^{20,21} these domains have only been examined prospectively in a handful of studies besides ours. Deficits were found on the Sequential scale (tapping working memory) of the Kaufman Assessment Battery for Children^{22,23} and the Test of Attentional Performance in one study.²⁴ However, the authors of another study (N = 18) did not find attention or executive function problems on the NEPSY-II.²⁵

In paired analyses, IQ, executive function, and math were stable over time. Thus, it appears that in pediatric liver transplantation survivors with below-average functioning, deficits may remain mostly static after the initial recovery period. This pattern is different from the impact of other brain insults on cognitive function in the pediatric population such as cancer patients, who experience decreasing performance over time with late effects of treatment,¹¹ or traumatic brain injury patients, who experience the most rapid improvement in functioning during the first 6–12 months, followed by much more gradual improvement/stabilization.¹² The few available studies in pediatric patients with kidney transplant suggest cognitive improvement in some areas after transplant compared with before transplant but fail to provide information regarding the developmental trajectory after transplantation.²⁶

The current findings also suggest assessment of pediatric liver transplantation survivors around the time of school entry may be adequate to identify most patients at long-term risk, so long as they are beyond the initial transplant recovery period (2 or more years after liver transplantation). In this study, only reading improved from T1 to T2. However, the reading task used (single word untimed reading) was quite rudimentary and likely was not sensitive enough to capture reading difficulties in the later grades. Receiving special education resources between T1 and T2 did not make participants more likely to improve in WRAT-4 reading or math scores. However, it is difficult to conclude that special education support did not make a difference because we do not have details such as the timing, amount, and quality of support and we presume that some participants who needed special education may not have received it.

Linear and logistic repeated measures regression models provided internal consistency regarding factors predicting FSIQ. Although visit was forced into the models, it was only marginally significant in the linear model and was not significant in the logistic model. Furthermore, paired comparisons across time were also negative. Of the three

socioeconomic indicators included in the analysis, household status and parent education had an important influence in both models. Single parent household at the time of transplantation predicted a FSIQ that was 10 points lower than patients with 2 adult care-providers and was associated with a 4-fold increased risk of FSIQ ≤ 85 . Having a primary care provider with a college education was protective and may offset other risk factors. In this analysis, we sought to identify medical factors that could be targeted in intervention trials to improve cognitive outcomes. Two medical factors were significant in the models. Growth failure at transplant has previously been associated with lower functional outcomes,^{4,9,23} and in this model had a moderate impact. Patients more than 2 SDs below the 50th percentile for weight at liver transplantation were predicted to have a FSIQ score almost 6 points lower and were 3 times more likely to have lower FSIQ than patients without growth failure. Nutritional deficiency and growth failure in infancy and early childhood have repeatedly been found to be associated with neuroanatomical abnormalities and cognitive deficits.^{27–29}

The association with blood transfused during the transplant operation was somewhat unexpected. Transfusion volume was included as a marker of surgical complexity/complications that might not have been otherwise captured in the SPLIT data collection. Operative time and cold ischemia time are included in SPLIT data collection but were not significantly associated with IQ. Transfusion requirements in this sample were similar to those of patients in the overall SPLIT registry, where blood transfusion is required by more than 80% of patients, with a mean transfusion requirement in excess of 60 mL/kg (unpublished SPLIT data). It is unclear whether operative transfusion volume was simply a marker for a less stable course during surgery or whether massive transfusion itself could have caused neurological injury.³⁰ Making that distinction would be fundamental in planning intervention strategies.

The primary limitation of this study was attrition between T1 and T2. However, nearly three-fourths did return, and these patients did not differ from those who did not return on medical or demographic variables. Another drawback is the use of different IQ measures at T1 and T2 because of the lower age limit of the WISC-IV. Although the same measure was used for all participants within each time point, structural differences between the measures could potentially confound comparisons between time points. However, the WPPSI-III and WISC-IV are correlated at a level ($r = 0.89$) that is “nearly as high as the WISC-IV test-retest correlation ($r = 0.93$),” and means were quite similar between the 2 in the standardization sample (eg, WPPSI-III FSIQ mean = 102.5 and WISC-IV FSIQ mean = 102.7).¹⁶ We used a narrow age range to reduce variability in presentation within the sample. Thus, patients were of similar age at testing and had all experienced liver disease and transplant within the first 4 years of life.

A caveat regarding the use of the BRIEF is that, by design, it is an indirect measure of EF using a survey format, and thus is subject to respondent bias. Nevertheless, this measure provides a preliminary look at EF after pediatric liver transplantation, and assesses real-life functioning. Additionally, the limited number of teacher BRIEFs at each time point resulted in an even smaller number available for longitudinal comparison. However, there was no difference between those that returned BRIEFs and those that did not in terms of basic

medical or demographic variables. Teacher input in this study highlighted problems that are less apparent in the home setting, likely due to the different demands at home and at school.

Finally, our modeling for risk factors for these cognitive outcomes must be considered exploratory because even with a focused and funded, multicenter study, we were only able to perform repeated testing in 93 patients. However, we believe our findings reveal important insights into potential risk factors that can be more rigorously analyzed in future prospective studies.

Although the majority of patients demonstrated average functioning, this study underscores persistent cognitive and achievement deficits through the elementary years in greater numbers than expected, and provides some insights into contributing factors. Potential future directions include closer examination of the process by which pretransplantation nutritional status and surgical factors impact cognitive function to determine whether their effects are modifiable. Likewise, recognition of demographic variables that place patients at a greater risk for cognitive deficits (single-parent households and lower parental education) could support development of targeted resources and interventions with the families who need them most. Longitudinal assessment with longer developmental follow-up and careful prospective collection of medical data via the use of large, multicenter designs will help determine whether these deficits indeed remain stable through adolescence and beyond in some pediatric patients with liver transplantation, and further elucidate risk factors. Finally, further examination of attention and executive function are needed, particularly because these areas may be good candidates for intervention (eg, stimulants and cognitive rehabilitation) as with other types of brain injury.³¹ Assessment of these domains should include both direct and indirect measures in order to provide the most complete picture.

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Glossary

BRI	Behavioral Regulation
BRIEF	Behavior Rating Inventory of Executive Function
EF	Executive Function (eg, organizational skills and working memory)
FOG	Functional Outcomes Group
FSIQ	Full Scale IQ
GEC	Global Executive Composite
MI	Metacognition index
PR	Perceptual Reasoning
PS	Processing Speed

SPLIT	Studies of Pediatric Liver Transplantation
T1	Time 1
T2	Time 2
VC	Verbal Comprehension
WISC-IV	Wechsler Intelligence Scales for Children, 4th edition
WM	Working Memory (on WISC-IV)
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, 3rd edition
WRAT-4	Wide Range Achievement Test, 4th edition

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Appendix

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Figure.

Comparison of liver transplant patients' FSIQ scores on the WISC-IV at T2 with the expected normal distribution (N = 92).

Table I

Variables included in univariate analyses

	Linear (continuous FSIQ)	Logistic (FSIQ 85)
Visit (T1 or T2)	0.0570*	0.2003*
Demographic variables		
Sex	0.0486*	0.0642*
Race	0.0049*	0.3970
Household status	<0.0001*	0.0009*
Parent education (primary caregiver)	0.0005*	0.0010*
Primary insurance	0.0021*	0.1752
Age at testing (continuous)	0.2003	0.1698
Pretransplant/disease severity variables		
Primary disease	0.0006*	0.7721
Height Z-score <-2 SD at LT	0.0120*	0.0471*
Weight Z-score <-2 SD at LT	0.0098*	0.0219*
History of FTT at LT	0.3918	0.1437
History of ascites at LT	0.2041	0.8761
History of variceal bleeding at LT	0.1525	0.1209
History of hepatic encephalopathy at LT	0.4283	0.7473
Hospitalization status at LT	0.0214*	0.0436*
Ever status 1	0.9804	0.3744
PELD score at LT (continuous)	0.0079*	0.0208*
Transplant variables		
Age at LT (continuous)	0.4654	0.5886
Number of liver transplantations	0.1093	0.1384
Donor type	0.0046*	0.0457*
Platelets (continuous)	0.4640	0.5940
Length of operation (continuous)	0.3344	0.6384
Cold ischemia time (continuous)	0.1570	0.0590*
Intraoperative transfusion requirement (continuous)	<.0001*	0.0003*
Primary calcineurin inhibitor at LT	0.8626	0.3304
Posttransplantation variables		
Transplant length of stay	0.1316	0.2659
Days hospitalized since last follow-up (continuous)	0.0310*	0.0448*
Reoperation in first 30 days post-LT	0.0297*	0.2546
Steroid Use in first 30 days post-LT	0.5843	0.6775
Calcineurin inhibitor at follow-up	0.4185	0.4271
Calcineurin inhibitor trough level at follow-up	0.4275	0.9656
Steroid use at follow-up	0.5532	0.6751

	Linear (continuous FSIQ)	Logistic (FSIQ 85)
Interval from LT to testing (continuous)	0.9505	0.2678

FTT, failure to thrive; *LT*, liver transplantation; *PELD*, pediatric end-stage liver disease.

* Variables that met criteria for inclusion in initial multivariate regression analyses for linear and logistic models. All variables are categorical unless otherwise noted.

Table II

Participant demographic and medical characteristics at T2 (n = 93)

	Median	Range
Age at testing, y	8.49	7.00–9.89
Age at LT, y	1.22	0.1–6.63
Interval from LT, y	6.87	2.40–9.10
PELD score at LT (9 missing)	12.64	–9.69–46.57
Height Z score at LT (4 missing)	–1.55	–7.80–3.41
Weight Z score at LT (11 missing)	–1.21	–8.27–2.14
	N	%
Female	49	52.7
Race (1 missing)		
White	55	59.8
Black	14	15.2
Hispanic	12	13.1
Other	11	11.9
Primary diagnosis		
Biliary atresia	56	60.2
Acute liver failure	8	8.6
Other cholestatic	13	14.0
Metabolic	8	8.6
Other	8	8.6
Status at transplantation		
ICU, intubated	11	11.8
ICU, not intubated	9	9.7
Hospitalized/no ICU	14	15.1
Not hospitalized	59	63.4
Number of liver transplantations		
1	86	92.5
>1	7	7.5
Donor		
Live	24	25.8
Whole	37	39.8
Technical variant	32	34.4
Household status (2 missing)		
Two-person household	75	82.4
One-person household	16	17.6
Education of primary caregiver (15 missing)		
Some HS or less	4	5.1
HS diploma/GED	15	19.2
Some college or more	59	75.7

	Median	Range
Primary insurance (13 missing)		
Private	38	47.5
US federal or state-funded	28	35.0
Provincial government (Canada)	12	15.0
Other	2	2.5

GED, general educational development; *HS*, high school; *ICU*, intensive care unit; *LT*, liver transplantation; *PELD*, pediatric end-stage liver disease.

Table III

Longitudinal comparison of cognitive and achievement scores at T1 (ages 5–6 years) and T2 (ages 7–9 years)

Variable	Mean $\pm$ SD at T1 (n)	Mean $\pm$ SD at T2 (n)
WPPSI-III/WISC-IV		
FSIQ	94.7 $\pm$ 13.5 (134)	92.1 $\pm$ 14.9 (91)
Verbal IQ/VC	95.0 $\pm$ 13.8 (134)	91.7 $\pm$ 14.5 (91)
Performance IQ/PR	94.9 $\pm$ 13.5 (134)	95.9 $\pm$ 15.4 (92)
PS	98.3 $\pm$ 15.7 (132)	95.1 $\pm$ 15.0 (92)
WM	NA	90.7 $\pm$ 14.6 (92)
WRAT-4		
Word Reading *	92.7 $\pm$ 17.2 (140)	98.2 $\pm$ 14.0 (93)
Math Computation	93.1 $\pm$ 15.4 (139)	90.1 $\pm$ 15.9 (93)
BRIEF Parent		
BRI	51.5 $\pm$ 11.3 (133)	50.2 $\pm$ 12.1 (92)
MI	52.3 $\pm$ 11.2 (130)	53.7 $\pm$ 12.2 (91)
GEC	52.3 $\pm$ 11.4 (130)	52.6 $\pm$ 12.1 (91)
BRIEF Teacher		
BRI	56.7 $\pm$ 15.2 (72)	53.5 $\pm$ 13.6 (61)
MI	58.2 $\pm$ 14.7 (70)	56.7 $\pm$ 12.1 (62)
GEC	58.1 $\pm$ 15.0 (70)	56.0 $\pm$ 12.7 (61)

NA, evaluated.

* Paired comparison analysis between T1 and T2 showed statistical significance only for Word Reading ($P = .0001$).

Note: WM is not evaluated on the WPPSI-III. T1 data reprinted with permission from Sorensen et al.⁵

Table IV

BRIEF subscales for parent report and teacher report at T2

BRIEF subscales	T2			
	N	Mean	SD	Adjusted significance level*
BRIEF parent subscales				
Inhibit	92	52.73	12.62	NS
Shift	92	49.03	11.11	NS
Emotional Control	92	48.61	11.28	NS
Initiate	92	52.48	11.50	NS
Working memory	92	55.40	11.92	NS
Plan/Organize	91	53.59	11.97	NS
Organization of Materials	92	53.10	9.87	NS
Monitor	92	51.00	11.90	NS
Brief teacher subscales				
Inhibit	62	53.52	13.84	.01
Shift	61	53.62	11.84	.01
Emotional Control	62	52.10	12.80	.01
Initiate	62	56.26	10.68	.02
Working memory	62	56.65	12.82	.02
Plan/Organize	62	55.61	12.87	.04
Organization Of Materials	62	56.31	12.70	.01
Monitor	62	55.97	12.53	.04

NS, not significant.

* χ^2 test for goodness of fit.

Table V

FSIQ as an outcome measure in linear and logistic regression models

Variable	Estimate	Lower 95% CI	Upper 95% CI	P value
Linear regression: FSIQ as continuous variable				
Intercept	97.59	91.90	103.29	<.0001
Visit				
Testing T1				
Testing T2	-2.25	-4.49	-0.002	.0498
Household status				
Two-person household				
One-person household	-10.04	-15.99	-4.10	.0011
Parental education status (overall $P = .0093$)				
HS grad/GED				
Some HS or less	-1.17	-9.31	6.97	.7759
Some college or more	6.95	1.68	12.22	.0102
Weight Z-score at LT				
Greater than negative 2 SD				
Negative 2 SD or below	-5.60	-10.38	-0.82	.0219
Blood transfusions, mL/kg	-0.06	-0.08	-0.03	<.0001
	OR	Lower 95% CI	Upper 95% CI	P value
Logistic regression: FSIQ ≥ 85				
Household status				
Two-person household				
One-person household	3.93	1.40	11.02	.0094
Parental education status (overall $P = .0021$)				
HS grad/GED				
Some HS or less	2.66	0.37	19.18	.3329
Some College or more	0.26	0.09	0.77	.0144
Weight Z-score at LT				
Greater than negative 2 SD				
Negative 2 SD or below	3.23	1.23	8.48	.0176
Blood transfusions, mL/kg	1.01	1.01	1.02	<.0001