Longitudinal Study of Cognitive and Academic Outcomes after Pediatric Liver Transplantation

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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 $P \leq .10$ 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.

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. *(J Pediatr 2014;165:65-72)*.

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

BRI	Behavioral Regulation	SPLIT	Studies of Pediatric Liver Transplantation
BRIEF	Behavior Rating Inventory of Executive Function	T1	Time 1
EF	Executive Function (eg, organizational skills and working memory)	T2	Time 2
		VC	Verbal Comprehension
		WISC-IV	Wechsler Intelligence Scales for Children, 4th edition
FOG	Functional Outcomes Group		
FSIQ	Full Scale IQ	WM	Working Memory (on WISC-IV)
GEC	Global Executive Composite	WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, 3rd edition
MI	Metacognition index		
PR	Perceptual Reasoning	WRAT-4	Wide Range Achievement Test, 4th edition
PS	Processing Speed		

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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 pretransplantation (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