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Health Related Quality of Life and Neurocognitive Outcomes in the First Year after Pediatric Acute Liver Failure

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Abstract

Objective—To determine health related quality of life (HRQOL) and neurocognitive impairment in SURVIVORS OF pediatric acute liver failure (PALF)

Study design—A longitudinal prospective study was conducted. At 6 and 12 months (6M, 12M) after PALF presentation, surveys of HRQOL were completed for 2–19 year olds, and executive functioning (EF) for ages 2–16. At 12M, patients 3–16 years completed neurocognitive testing. HRQOL scores were compared with a healthy, matched sample. Neurocognitive scores were compared with norms; EF scores were examined categorically.

Results—52 parent-report HRQOL surveys were completed at 6M, 48 at 12M; 25 patients completed neurocognitive testing. The median age at 6M was 7.9 years (range 3.5–15.0), and final diagnosis was indeterminate for 46.2% (n=24). Self and parent-report on PedsQL™ Generic and Multidimensional Fatigue scales fell below the healthy sample at 6M and 12M (almost all $P <$

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001). Children reported lower mean scores on cognitive fatigue at 12M (60.91 ± 22.99) compared with 6 M (73.61 ± 27.49 , $p=0.006$). The distribution of Behavior Rating Inventory of Executive Function scores was shifted downward on parent-report (preschool) for all indices at 6M ($n=14$, $p=0.003$); Global Executive Composite and Emergent Metacognition at 12M ($n=10$, $p=0.03$). Visual Motor Integration (VMI-6) Copying (mean= 90.3 ± 13.8 , $p=0.0002$) and VMI-6 Motor Coordination (mean= 85.1 ± 15.2 , $p=0.0002$) fell below norms, but full scale IQ (Wechsler Scales) and Attention (Conners' Continuous Performance Test) did not.

Conclusions—survivors of PALF appear to show deficits in motor skills, EF, HRQOL, and evidence for worsening cognitive fatigue from 6M to 12M following PALF presentation.

Keywords

Cognition disorders; executive functioning; pediatric liver disease; pediatric liver transplantation; cognitive fatigue

Pediatric acute liver failure (PALF) is a rare, devastating condition affecting often previously healthy children and associated with 50% spontaneous survival. Rapid clinical deterioration frequently occurs, with hepatic encephalopathy (HE) and multi-system organ failure. Cerebral edema (CE) associated with advanced injury can result in intracranial hypertension and brain herniation.(1) (2) (3) A small case series of children surviving PALF secondary to viral hepatitis demonstrated significant cognitive deficits that improved in parallel with indicators of CE and circulating pro-inflammatory cytokine levels. (4)

Prospective neurocognitive testing has been lacking in a cohort of PALF survivors of varied etiology. Many PALF patients who require LT report cognitive fatigue affecting day-to-day function. (5) Spontaneous survivors of PALF are also likely at increased risk for cognitive fatigue, but clinical follow-up after discharge is inconsistent. Despite resolution of HE in survivors, there may be residual sub-clinical neurological injury compromising neurocognitive function, including cognitive fatigue. Cognitive fatigue has been operationally defined as a “decline in alerting, orienting, and executive attention performance” as distinct from general fatigue (eg, feeling tired). (6) Health related quality of life (HRQOL) in these survivors may also be lower than expected compared with healthy children. Detailed assessment of neurocognitive function, cognitive fatigue, and HRQOL is critical to understanding the full impact of PALF.

A prior cross-sectional study of neurocognitive and HRQOL outcomes in PALF survivors with varied etiology was conducted by the Pediatric Acute Liver Failure Study Group (PALFSG). Thirty-six patients aged 6–16 were assessed 1–6 years after presentation. This study demonstrated average IQ, but greater than expected impairments in motor skills, attention, executive functioning (EF), HRQOL and cognitive fatigue in long-term survivors. (7)

The goal of the present longitudinal prospective study, also conducted by the PALFSG, was to characterize more fully in PALF survivors during the first year following presentation and to validate findings from our cross-sectional study. We hypothesized HRQOL and cognitive fatigue would be lower at 6 months (6M) and 12 months (12M) after PALF presentation

compared with a matched healthy sample, but would improve from 6M to 12M. We also hypothesized neurocognitive function (specifically motor, attention, and EF) would be lower compared with test norms at 12M after PALF.

METHODS

PALFSG inclusion criteria are: age birth to <18 years, biochemical evidence of acute liver injury without chronic liver disease, and coagulopathy not corrected by parenteral vitamin K or other intervention. Registry participants must have liver synthetic failure with international normalized ratio ≥ 1.5 associated with HE, or international normalized ratio ≥ 2.0 with or without HE.

Eligible patients for the present longitudinal study were drawn from the PALFSG (N=158) and recruited at 12 medical centers in the United States and Canada between May 2012 and December 2014, with one year follow up testing through December 2015. None of the patients in the current sample participated in the previously published cross-sectional study. (7) Specific eligibility criteria differed slightly for HRQOL and neurocognitive/EF testing due primarily to the measures used. Therefore, the samples overlap, but are not the same. The Figure (available at www.jpeds.com) details the recruitment algorithm and the reasons for nonparticipation.

HRQOL and Fatigue

Eligible patients from 2 to 19 years of age enrolled in the PALFSG completed age-appropriate HRQOL and cognitive fatigue surveys at 6M (N=52; 81 % of eligible) and 12M (N=48; 84% of eligible) following PALF presentation. Subject and parent/guardian were fluent in English or Spanish.

The healthy sample was derived from 2 previously completed studies (8) (9) and randomly matched by age, sex, and race/ethnicity to the PALF sample separately for child self-report and parent-proxy report given age differences between the two.

Executive Function and Neurocognitive Function

Surveys assessing EF were completed by parents of eligible patients age 2 to 16 years at 6M (N=31; 89% of eligible) and 12M (N=25; 89% of eligible) after PALF presentation. Eligible patients age 3–16 years completed neurocognitive testing 12M after PALF presentation (N=25; 89% of eligible). In addition, participants (≥ 8 years old) and parents completed the depression and PTSD surveys along with the neurocognitive testing battery.

Eligibility for the present study was assessed at the PALFSG visit. Therefore, if the visit was missed, eligibility could not be determined. Participants and parent/guardian were fluent in English. Exclusions included unstable medical status at time of testing (eg, hospitalizations within 4 weeks prior to testing, awaiting LT, uncontrolled seizures) or medical factors that could independently affect functioning or invalidate testing (ie, cancer diagnosis; weakness or abnormality of muscle tone or coordination, sufficiently severe that it impaired the ability to perform the physical tasks required for testing; no intelligible speech and/or inability to follow simple commands.) Fourteen children met exclusion criteria at the 12M visit: non-

English speaking (n=5), hospitalized or listed for LT (n=5), impaired speech or muscle weakness (n=3) and previous cancer diagnosis (n=1).

Study Design

Participants meeting inclusion criteria were identified by the Data Coordinating Center, which provided weekly reports to site coordinators and investigators of those patients who were due for their 6M and 12M follow-up visits. The report served as a notice for coordinators to begin scheduling the patient for an in-person follow-up visit with the appropriate amount of time and resources for the visit specific measures to be completed. The 12M neurocognitive tests were performed or supervised by licensed psychologists.

Written, informed consent was obtained from the child's parent/legal guardian before participation in the PALFSG. Assent was obtained from children as required by individual institutions. The study protocol was approved by the institutional review boards at all PALFSG sites.

Instruments

Health Related Quality of Life and Fatigue (Completed at 6M and 12M visit)—

The child self-report (only for 5 years old) and parent proxy-report versions of the 23-item PedsQL4.0 Generic Core Scales (PedsQL, Mapi Research Institute, Lyon, France) (8) and the PedsQL Multidimensional Fatigue Scale (MFS) (10) (11) were administered at both the 6M and 12M follow-up visits. Items are reverse-scored and linearly transformed to a 0–100 scale, so that higher scores indicate better HRQOL. The PedsQL encompasses 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items) and were developed through focus groups, cognitive interviews, pre-testing, and field testing measurement development protocols. The PedsQL MFS is an 18-item instrument encompassing 3 scales: (1) General Fatigue (6 items, e.g., “I feel tired.”; “I feel too tired to do things that I like to do.”), (2) Sleep/Rest Fatigue (6 items, eg, “I feel tired when I wake up in the morning.”; “I rest a lot.”), and (3) Cognitive Fatigue (6 items, e.g., “It is hard for me to keep my attention on things.”; “It is hard for me to remember what people tell me”). The PedsQL MFS Cognitive Fatigue sub-scale correlates well with EF deficits, particularly Working Memory as measured by the Behavior Rating Inventory of Executive Function (BRIEF) in children following LT (12).

Executive Function (Completed at 6M and 12M visit)—Parents of children 2 years and older completed age appropriate versions of the Behavior Rating Inventory of Executive Function (BRIEF) at the 6M and 12M visit. (13) The BRIEF is a survey of symptoms related to attention and EF that yields composite scores including the Global Executive Composite, the Metacognition Index and the Behavioral Regulation Index. This scale offers the opportunity to quantify observations of naturalistic behaviors related to EF that are difficult to assess in a formal testing situation. The BRIEF – Preschool Version is designed for use with age 2–5 years and yields a Global Executive Composite, as well as three broad indices: Inhibitory Self Control, Flexibility, and Emergent Metacognition (14). Participants ages 11 and older also completed the BRIEF-Self Report (15).

Neurocognitive Function (Completed at 12M visit)

Intelligence Quotient: To assess general intellectual reasoning abilities, participants aged 3 years through 5 years 11 months 30 days completed the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV).⁽¹⁶⁾ The WPPSI-IV provides index scores in the following areas: Full Scale IQ, Verbal Comprehension, Visual Spatial, and Working Memory, for children age 2–3. Additional composites for age 4–7 include Fluid Reasoning, Processing Speed, and Cognitive Proficiency. The WPPSI-IV is a psychometrically sound measure with reliability estimates ranging from 0.91 to 0.96 for all composite scores except Visual Spatial Index (0.89) and Processing Speed Index (0.86).

The Wechsler Intelligence Scales for Children-4th edition (WISC-IV) ⁽¹⁷⁾ was administered to participants aged 6 years through 16 years 11 months 30 days. It is comprised of four primary indices similar in content to the WPPSI-V: Full Scale IQ, Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. The WISC-IV is also psychometrically strong, with reliability estimates ranging from 0.88 to 0.97 for composite scales. WPPSI-IV and WISC-IV Full Scale IQ, Verbal Comprehension, Visual Spatial/Perceptual Reasoning, and Fluid Reasoning/Perceptual Reasoning Indices are highly correlated (corrected $r = 0.84, 0.73, 0.75, 0.77$, respectively), with more moderate correlations for Working Memory (corrected $r = 0.55$) and Processing Speed (corrected $r = 0.60$).

Adaptive Skills: Parents of children 3 years and older completed the Adaptive Behavior Assessment System-Second Edition (ABAS-II) ⁽¹⁸⁾. Adaptive skills, also referred to as “independent living skills,” are life tasks that can be completed with increasing degrees of independence as the child develops. On the ABAS-II, adaptive skills are assessed across several areas including communication, community functioning, social skills, self-care, and home living skills.

Visual Spatial and Visual Motor Ability: Participants ages 3 and older also completed the Beery-Buktenica Developmental test of Visual-Motor Integration, 6th Edition (VMI-6) ⁽¹⁹⁾. The VMI-6 is a measure that uses abstract designs to assess visual perception (matching), motor skills (tracing emphasizing speed and precision), and visual-motor integration (copying).

Attention: Participants ages 4 and older completed age appropriate versions of the Conners’ Continuous Performance Test II (CPT-II) ⁽²⁰⁾, a computerized test of sustained attention that involves responding to targets (all letters except “x”) by pressing the space bar as quickly as possible and inhibiting responses to infrequent distracters (“x”). Various aspects of performance are recorded including reaction time speed, variability and standard error, number of omissions (missed targets), and commissions (erroneous responses to distracters). The Conners’ Kiddie Continuous Performance Test (K-CPT) ⁽²¹⁾ is based on the CPT-II and yields the same scores, but is designed for children age 4–5 and requires recognition of pictures rather than letters.

Depression and Post Traumatic Stress Disorder (Completed at 12M visit): The Children's Depression Inventory, Second Edition (CDI-2) (22), a standardized survey assessing symptoms of depression, was completed by parents and children who were at least 8 years of age. Simply worded, multiple-choice questions asked respondents to rate the presence/severity of various indicators of depressed mood (eg., difficulties with sleep, appetite, feelings of sadness). CDI-2 Parent and self-report yield a total score and two scale scores (Emotional Problems and Functional Problems).

Participants 8 years of age and older and their parents completed the Abbreviated UCLA Post Traumatic Stress Disorder - Reaction Index (23) This is a nine item instrument that can help screen for PTSD after any type of trauma exposure. The abbreviated version has good convergent validity and excellent sensitivity (0.93) and specificity (0.87) for detecting PTSD diagnosis. Children should be considered to have clinically significant PTSD symptoms with a score of 10 or higher and subsequently, offered a mental health care referral.

Statistical Analyses

Descriptive statistics were generated for demographic and clinical patient variables and are reported as medians and 25th and 75th quartiles for continuous variables and frequencies/proportions for categorical variables.

To assess whether participants had worse HRQOL and symptoms of fatigue than average, independent-samples t tests were used to compare our sample with a matched sample of healthy children. Effect sizes were calculated to determine the magnitude of the differences. Effect size as utilized in these analyses was calculated by taking the differences between the groups' sample means, divided by the pooled standard deviation (SD). Effect sizes for differences in means are designated as small (0.20), medium (0.50), and large (0.80) (24). The overall Type I error rate was maintained at 0.05 by the Hochberg adjustment for multiple comparisons (25). An adjustment was made separately for each instrument, and separately by respondent on survey measures.

EF data were compared with the normal population by dividing it into categories based on the population mean of 50 and SD of 10, categories were > 70, 61–70, 51 –60, and 50. A chi-square (X^2) goodness of fit test was used to determine if the two groups were different. Reported effect sizes were calculated using Cohen's W. For these data, using a nominal alpha level of 0.05 with a sample size of 14, a minimum effect size of 0.88 could be detected with 80% power.

The data from the WPPSI-IV/WISC-IV, VMI-6, and ABAS-II (mean=100, SD=15 for test norms), and CPT-II/K-CPT (mean=50, SD=10 for test norms; higher scores are worse) were compared with the normal population using X^2 and Kolmogorov-Smirnov goodness of fit tests. In the categorical comparison, a sample size of 25 and a nominal p-value of 0.05 and 80% power an effect size of 0.66 or larger could be detected. For the continuous comparison, 1000 bootstrap simulations were performed to estimate the detectable effect size. A sample size of 25 with a nominal alpha of 0.05 and standard deviation of 16 provided 82% power to detect a difference of 10 between the normal population mean of 100 and the sample mean. For the CPT-II/K-CPT measures, using a sample size of 19, standard deviation of 10 and

nominal alpha of 0.05, 1000 simulations estimated power at 79% to detect a difference of 7 between the normal population mean of 50 and the sample mean.

The overall type I error rate was maintained at 0.05 by the Hochberg adjustment for multiple comparisons (25). T-tests were used to evaluate relationships between Motor Coordination score and baseline variables of interest and maximum HE. Pearson correlation was used to assess association between age and Motor Coordination. Previously selected key demographic and relevant medical factors were evaluated to determine relationships with parent-proxy report and self-report PedsQL™ MFS Cognitive Fatigue sub-scale scores. These associations were evaluated using a generalized linear mixed model with a random intercept to account for repeated measures of fatigue in patients. Statistical analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS Version 15.0 for Windows (Microsoft Inc., Redmond, WA, USA). Power and effect size calculations were carried out using PASS (NCSS, LLC., Kaysville, UT, USA) and G*Power 3.1.7.(26)

Results

Of the 52 patients completing HRQOL surveys at 6M, 70.2% were white, and 78.1% had parents with some college or postsecondary education. Proxy respondents included 32 mothers (78.0%), 8 fathers (19.5%), and 1 guardian (2.5%). The median age at 6M was 7.9 years (range 3.5 – 15.0). The final diagnosis was indeterminate for 46.2% (n=24). A maximal grade III or IV HE was documented in 17.3% of the sample (n=9) during hospitalization. Medical record review indicated that 46.2% (n=24) had received LT prior to the 6M follow-up (n=23 within 30 days of presentation, n=1 at 120 days); one patient received LT after the 6M follow-up visit (185 days). Table I (available at www.jpeds.com) provides descriptive statistics for participants on select demographic and medical variables.

Of the 25 patients completing the neurocognitive testing at 12M, 56.0% (n=14) were male, 81.8% (n=18) were white, and 80% of parents had some college or postsecondary education. Proxy respondents included 18 mothers (72.0%) and 7 fathers (28.0%). A maximal grade III or IV HE during hospitalization was documented in 28.0% (n=7) of the sample and 52.0% (n=13) received LT. Twelve patients were transplanted within the first 16 days of PALF presentation, and 1 patient after the 6M follow-up visit (185 days).

Health Related Quality of Life and Fatigue (Completed at 6M and 12M visit)

Table 2 presents the means and SDs of the PedsQL for the study sample and the matched healthy children sample. For each scale and summary score, the study sample for both child self-report and parent proxy-report at the 6M and 12M visits reported significantly lower HRQOL than healthy children. Most effect sizes ranged from medium to large, with the largest found in Physical Health (1.17) and Total Score (1.10) on the child self-report. Table 3 presents the means and SDs of the PedsQL MFS sub-scales for the study sample and the sample of matched healthy children. For both child self-report and parent proxy-report at 6M and 12M, sub-scale scores were significantly lower for the study group, also with medium to large effect sizes. The largest difference was noted in child self-report Total Fatigue.

Child self-report paired comparisons between 6M and 12M

We identified 2 key child self-report scales with large effect sizes for comparison at the 6M and 12M follow-up. For the 21 cases in which child self-report were available at 6M and 12M, paired t-tests were conducted on the PedsQL Physical Health score and the PedsQL MFS Cognitive Fatigue sub-scale score. The child self-report Physical Health scores were significantly different between the 6M and 12M follow-up visits with children reporting lower scores at 12M (75.45 ± 17.99) compared with 6M (83.78 ± 13.28) ($p=0.016$). Additionally, children reported a lower mean score on the PedsQL MFS Cognitive Fatigue sub-scale at 12M (60.91 ± 22.99) compared with 6M (73.61 ± 27.49) ($p=0.006$). Parent proxy-report data for only the children who could self-report ($n=20$) also showed a decline at 12M (60.21 ± 25.34) as compared with 6M (71.46 ± 25.30) ($p=0.02$).

Factors Associated with Cognitive Fatigue Outcome

Multivariable analysis was conducted to examine the impact of selected variables on cognitive fatigue scores by child self-report ($n=55$ observations, 34 participants) and parent proxy-report ($n=95$ observations, 60 participants). Variables included age category at PALF presentation, follow-up interval from PALF presentation, parental education, LT, intubation during the PALF event, and maximal grade of HE (Tables 4 and 5; available at www.jpeds.com). The only significant variable in the final model was follow-up interval. Child self-report cognitive fatigue scores at 12M were significantly lower than 6M ($p=0.01$). The parent-proxy report analysis included an additional 26 children less than age 5 years who did not self-report HRQOL. The same trend toward lower scores at 12M was observed in the parent proxy-report analysis, but the difference did not reach statistical significance and no other variables emerged as significantly associated with cognitive fatigue ($p=0.07$).

Executive Function (Completed at 6M and 12M visit)

The BRIEF preschool age ($n=14$) and school age ($n=17$) parent report were completed at the 6M follow-up. The distribution of BRIEF composite scores was shifted downward on the preschool age report for all indices at 6M compared with test norms ($p=0.003$) (Table 6). The BRIEF preschool age ($n=10$) and school age ($n=16$) parent reports were also completed at the 12M follow-up. On the preschool age reports at 12M, participants demonstrated a higher proportion of elevated concerns on the Global Executive ($p=0.03$) and Emergent Metacognition ($p=0.03$) composite scales compared with test norms. There were no significant differences among distributions compared to test norms for the 6M or 12M school age parent reports. In addition, the BRIEF self-reports at 6M ($n=13$) and 12M ($n=12$) showed no significant differences compared with norms.

Neurocognitive Function (Completed at 12M visit)

Table 7 summarizes intelligence, visual spatial/visual motor ability, and attention scores for the 25 patients that completed neurocognitive testing at 12M. There were no significant differences compared with norms on the WISC-IV/WPPSI-IV, ABAS-II, or CPT- II/K-CPT. However, patients scored significantly lower than test norms on Visual Motor Integration and Motor Coordination components of the VMI-6 ($p=0.0002$ and $p=0.0002$, respectively). The distribution of participant scores for the Motor Coordination subscale indicates that

more participants than expected had worse motor skills than in the normal population ($p=0.0006$). There was no significant difference in the distribution of participant scores in the Visual Motor Integration subscale.

Factors Associated with Motor Coordination

Univariable analysis was performed using Motor Coordination as a continuous dependent variable and LT, highest parental education, HE at PALF presentation, and maximal grade of HE during hospitalization as the independent variables (Table 8; available at www.jpeds.com). None of the variables were significantly associated with Motor Coordination. The correlation of Motor Coordination with age at testing was also not significant ($p=0.93$). Finally, the association of final diagnosis category (acetaminophen (APAP) overdose, indeterminate and other) to Motor Coordination score was not significant ($p=0.46$).

Depression and Post Traumatic Stress Disorder

Thirteen participants were old enough to complete the CDI-2 and PTSD-Reaction Index. The mean score for child self-report on the CDI-2 Total score was 53.15 ± 14.1 . Of the 13 participants, 15.4% (APAP overdose $n=1$, autoimmune hepatitis $n=1$) had T-scores ≥ 70 , consistent with clinically significant depressive symptoms. 38% (5) children had a score of 10 or higher on the PTSD-Reaction Index self-report. One of these also had a CDI-2 Total score ≥ 70 and two had a final diagnosis of APAP overdose.

Discussion

The present study characterized functional outcomes in children with PALF. This prospective, multicenter analysis of neurocognitive outcomes has significant implications for planning rehabilitation and setting expectations for survivors and their families. Our findings suggest that within the first year of recovery, PALF survivors may experience worse HRQOL and increased cognitive fatigue compared with healthy children. Our results also provide some evidence for a higher prevalence of motor and EF deficits in PALF survivors compared with the normal population.

Several small, single center studies in PALF survivors have examined cognitive function in specific disease groups including acute viral hepatitis (4), Wilson disease (27), and Reye syndrome (28), but these findings are difficult to generalize to the broader group of diagnoses that lead to PALF. Srivastava et al examined 6 children with HE and CE demonstrated on advanced MRI and correlated findings with serial neurocognitive testing after recovery. (4) Although scores within 3 months following PALF were significantly lower than norms, they demonstrated significant improvement at follow-up 4 to 7 months post event. At that point, scores were no longer significantly different from norms. We previously conducted a cross-sectional study of long-term survivors which included an array of diagnoses, but in that analysis, it was not possible to determine whether observed and reported deficits were static or improving. (7)

Our results further validate findings from the previous PALFSG cross-sectional study, which found similar results in a separate sample of survivors who returned for testing up to 6 years

after illness. (7) Both this current longitudinal and the previous cross-sectional study included a high proportion of LT recipients, confounding whether the findings are more representative of PALF survivors with LT than without. Multi-center analysis of LT recipients at similar survival intervals suggest LT survivors, most of whom had chronic liver disease, have more extensive neurocognitive impairment (29) including lower than expected IQ. (29) The measured and reported deficits in this PALF cohort were less severe, without any significant differences in IQ noted.

In this longitudinal study, HRQOL was significantly lower than a matched sample of healthy children. Total scores from both child and parent-reports were similar to results in long-term follow-up after LT and in children with a variety of chronic diseases.(30) Effect sizes for child self-report scores were largest for Physical and School Function sub-scales on the PedsQL™ and for General and Cognitive Fatigue sub-scales on the PedsQL MFS. In a comparison of child-reported Physical and Cognitive Function at 6M versus 12M, patients reported lower function in both domains at 12M even though there were few significant health events in patients between testing intervals. We expected HRQOL would improve at increasing interval from the PALF event as such improvement over time has been noted in both LT and critical care survivor cohorts.(31–33) However, there was a meaningful decrease in physical and cognitive function scores from both the child and parental perspectives. Child self-report physical function scores at 12M in this study appear lower than a previous report of recipients at 12–24 months post LT. (34) It is unclear whether patients may experience a sense of decline during the second half of the first year following the event because of expectations associated with normal daily activities, including school return to pre- event levels. We speculate that there may be rebound during the second year post LT because scores in the previous cross-sectional study more closely resembled the 6M scores in this longitudinal study.(7)

We chose to explore predictors of cognitive fatigue as function in this domain is expected to have an important impact on school reintegration and performance. Furthermore, in prior studies in pediatric LT recipients, our group has found significant correlation between cognitive fatigue scores and EF (especially working memory) as tested on the BRIEF. (12) Thus, cognitive fatigue scores may reflect this dimension of cognitive function as well. The only significant predictor was follow-up interval from PALF presentation. Younger children did have lower than expected BRIEF scores, but EF did not appear impaired in school age participants. HE was not a predictor of cognitive fatigue, and the only predictor of fatigue in this group was longer interval from the PALF presentation. These findings suggest PALF survivors, with or without LT, may be at risk for problems related to EF (such as working memory), especially in early childhood. Given the small sample size, it is also possible the sample was not large enough to detect significant differences at the older age in this study.

One year after PALF, survivors have lower than expected motor coordination and visual motor integration. Our expectation was children with advanced HE would be at higher risk for motor impairments. Although children with a grade III or IV HE may not always demonstrate CE on imaging (4), CE is much more common in that setting. Irreversible motor cortex injury is expected to be more likely when CE is well established, but even sub-clinical CE may have an impact. Univariate analysis failed to show an association between

maximal level of HE and motor deficits. Because these patients did not consistently receive imaging, it was impossible to identify those with sub-clinical CE and thus, CE could not be assessed as a risk factor. We also considered LT as a risk factor. A recent analysis of motor function in pediatric LT recipients revealed 29% of recipients had motor impairment that did not improve over time in long-term follow-up after transplant. (35). Because one-half of our study cohort received transplantation, we tested whether these deficits were related to transplantation and found no significant association. Our inability to identify risk factors for this impairment is likely due to a lack of sensitive tools to assess cortical injury during the acute event, or small sample size.

The greatest limitation to our study is indeed small sample size, which limits power to detect small differences, and therefore findings must be cautiously interpreted. In part, this was due to age limits; many PALFSG patients fell below age 3 at 12M following PALF presentation. Patients were recruited from 12 sites across the country and there was a robust reminder system to alert coordinators of eligibility windows to maximize participation. Nevertheless, some patients who were possibly eligible for testing did not return for the 12M clinical visit for the PALFSG. It is possible these patients were doing better, and did not feel the need to return. Small samples are subject to bias and, in fact, a high proportion of participants lived in households with indicators of high socio-economic status. This must be considered when generalizing findings to the broader group of children who survive PALF. In the current study, results from patients completing neurocognitive testing were variable; such may be due to small sample size and the use of various age-specific versions. Our study design emphasized rigorous neuropsychological testing. However, newer testing methods that leverage computer adapted algorithms to assess cognitive function may allow patients to report outcomes without returning to the medical center. These methods should be considered for future studies in this population.

In summary, PALF survivors have lower HRQOL than healthy children during the first year of recovery and evidence for worsening cognitive fatigue from 6M to 12M following PALF presentation. They also appear to be at risk for EF and motor deficits. Risk factors for HRQOL and neurocognitive impairments are not clear. Additional prospective studies of PALF survivors are needed to further explore predictors and longitudinal trajectories in order to inform clinical care, minimize modifiable risks, and support patients/families through this challenging experience.

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List of Abbreviations and Acronyms

APAP	Acetaminophen
ABAS-II	Adaptive Behavior Assessment System-Second Edition
BRIEF	Behavior Rating Inventory of Executive Function
CDI-2	Children's Depression Inventory, Second Edition
CPT-II	Conners' Continuous Performance Test II
K-CPT	Conners' Kiddie Continuous Performance Test
HE	Hepatic encephalopathy
HRQOL	Health related quality of life
PALF	Pediatric acute liver failure
PALFSG	Pediatric acute liver failure study group
PedsQL	PedsQL 4.0 Generic Core Scales
PedsQL MFS	PedsQL Multidimensional Fatigue Scale
PTSD	Post-traumatic stress disorder
SD	Standard deviation
WISC-IV	Wechsler Intelligence Scales for Children-4th edition
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition
VMI-6	Beery-Buktenica Developmental test of Visual-Motor Integration, 6 th Edition

Appendix

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References

1. Bemeur C, Butterworth RF. Liver-brain proinflammatory signaling in acute liver failure: role in the pathogenesis of hepatic encephalopathy and brain edema. *Metab Brain Dis.* 2013; 28:145–150. [PubMed: 23212479]
2. Dhawan A. Etiology and prognosis of acute liver failure in children. *Liver Transpl.* 2008; 14(Suppl 2):S80–84. [PubMed: 18825678]
3. Squires RH Jr. Acute liver failure in children. *Semin Liver Dis.* 2008; 28:153–166. [PubMed: 18452115]
4. Srivastava A, Yadav SK, Borkar VV, Yadav A, Yachha SK, Thomas MA, et al. Serial evaluation of children with ALF with advanced MRI, serum proinflammatory cytokines, thiamine, and cognition assessment. *J Pediatr Gastroenterol Nutr.* 2012; 55:580–586. [PubMed: 22614112]
5. Alonso EM, Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, et al. Cross-sectional analysis of health-related quality of life in pediatric liver transplant recipients. *J Pediatr.* 2010; 156:270–276. e271. [PubMed: 19846110]
6. Holtzer R, Shuman M, Mahoney JR, Lipton R, Verghese J. Cognitive fatigue defined in the context of attention networks. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn.* 2011; 18:108–128. [PubMed: 21128132]
7. Sorensen LG, Neighbors K, Zhang S, Limbers CA, Varni JW, Ng VL, et al. Neuropsychological functioning and health-related quality of life: pediatric acute liver failure study group results. *J Pediatr Gastroenterol Nutr.* 2015; 60:75–83. [PubMed: 25250681]
8. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Medical care.* 2001; 39:800–812. [PubMed: 11468499]
9. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr.* 2003; 3:329–341. [PubMed: 14616041]

10. Varni JW, Burwinkle Tasha M, Katz Ernest R, Meeske Kathy, Dickinson Paige. The PedsQL™ in Pediatric Cancer: Reliability and Validity of the Pediatric Quality of Life Inventory™ Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer*. 2002; 94:2090–2106. [PubMed: 11932914]
11. Panepinto JA, Torres S, Bendo CB, McCavit TL, Dinu B, Sherman-Bien S, et al. PedsQL Multidimensional Fatigue Scale in sickle cell disease: feasibility, reliability, and validity. *Pediatric blood & cancer*. 2014; 61:171–177. [PubMed: 24038960]
12. Varni JW, Limbers CA, Sorensen LG, Neighbors K, Martz K, Bucuvalas JC, et al. PedsQL Cognitive Functioning Scale in pediatric liver transplant recipients: feasibility, reliability, and validity. *Qual Life Res*. 2011; 20:913–921. [PubMed: 21184184]
13. Gioia, G., Isquith, P., Guy, S., Kenworthy, L. Behavior Rating Inventory of Executive Function. Odessa, FL: Psychological Assessment Services, Inc.; 2000.
14. Gioia, GA., Espy, KA., Isquith, PK. Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P). Lutz, FL: Psychological Assessment Resources, Inc.; 2005.
15. Guy, SC., Isquith, Peter K., Gioia, Gerard A. Behavior Rating Inventory of Executive Function-Self Report Version (BRIEF-SR). Odessa, FL: Psychological Assessment Resources, Inc.; 2004.
16. Wechsler, D. Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition technical and interpretative manual. San Antonio, TX: Psychological Corp.; 2012.
17. Wechsler D. Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV). San Antonio: The Psychological Corporation; 2003.
18. Harrison, P., Oakland, Thomas. Adaptive Behavior Assessment System - Second Edition (ABAS-II). Pearson; 2003.
19. Beery, KE., Buktenica, Norman A., Beery, Natasha A. Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition (Beery VMI). San Antonio: Pearson; 2010.
20. Conners, KC. Conners' Continuous Performance Test II Version 5. Multi-Health Systems; 2004.
21. Conners, KC. Conners' Kiddie Continuous Performance Test (K-CPT). North Tonawanda, NY: Multi-Health Systems, Inc.; 2004.
22. Kovacs, M., Staff, MHS. Children's Depression Inventory 2nd Edition (CDI-2). North Tonawanda, NY: Multi-Health Systems; 2011.
23. Steinberg AM, Brymer MJ, Decker KB, Pynoos RS. The University of California at Los Angeles Post-traumatic Stress Disorder Reaction Index. *Curr Psychiatry Rep*. 2004; 6:96–100. [PubMed: 15038911]
24. Cohen, J. Statistical Power Analysis for the Behavioral Sciences. 2. Hillsdale, NJ: Erlbaum; 1988.
25. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. *Statistics in Medicine*. 1990; 9:811–818. [PubMed: 2218183]
26. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007; 39:175–191. [PubMed: 17695343]
27. Hegde S, Sinha S, Rao SL, Taly AB, Vasudev MK. Cognitive profile and structural findings in Wilson's disease: A neuropsychological and MRI-based study. *Neurology India*. 2010; 58:708–713. [PubMed: 21045492]
28. Meekin SL, Glasgow JFT, McCusker CG, Rooney N. A long-term follow-up of cognitive, emotional, and behavioural sequelae to Reye syndrome. *Developmental Medicine and Child Neurology*. 1999; 41:549–553. [PubMed: 10479043]
29. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM, et al. Cognitive and academic outcomes after pediatric liver transplantation: Functional Outcomes Group (FOG) results. *American Journal of Transplantation*. 2011; 11:303–311. [PubMed: 21272236]
30. Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, Varni JW, et al. Health-related quality of life in pediatric liver transplant recipients compared with other chronic disease groups. *Pediatr Transplant*. 2011; 15:245–253. [PubMed: 21199214]
31. Colville GA, Pierce CM. Children's self-reported quality of life after intensive care treatment. *Pediatr Crit Care Med*. 2013; 14:e85–92. [PubMed: 23337805]

32. Cunha F, Mota T, Teixeira-Pinto A, Carvalho L, Estrada J, Marques A, et al. Factors associated with health-related quality of life changes in survivors to pediatric intensive care. *Pediatr Crit Care Med*. 2013; 14:e8–15. [PubMed: 23249784]
33. Cole CR, Bucuvalas JC, Hornung RW, Krug S, Ryckman FC, Atherton H, et al. Impact of liver transplantation on HRQOL in children less than 5 years old. *Pediatr Transplant*. 2004; 8:222–227. [PubMed: 15176957]
34. Feldman AG, Neighbors K, Mukherjee S, Rak M, Varni JW, Alonso EM. Impaired physical function following pediatric LT. *Liver Transpl*. 2016; 22:495–504. [PubMed: 26850789]
35. Almaas R, Jensen U, Loenneken MC, Tveter AT, Sanengen T, Scholz T, et al. Impaired motor competence in children with transplanted liver. *J Pediatr Gastroenterol Nutr*. 2015; 60:723–728. [PubMed: 25658058]

Figure 1.

158 participants were enrolled in the PALF cohort during the study period. Of 80 patients eligible to complete HRQOL surveys at 6 months, 64 attended follow-up visits and 52 completed surveys. At 12 months, 83 were eligible for HRQOL; 57 attended follow-up visits, 48 with completed surveys. At 6 months, 62 patients were in the appropriate age range to complete executive function surveys. Of 35 who attended the visit and met eligibility, 31 completed surveys. At 12 months, 59 patients were in the appropriate age range for neurocognitive testing, 28 attended the follow up visit and were found eligible, and 25 completed test

Table 1

Participant demographic and medical characteristics

Characteristic	HRQOL 6M (N=52)		HRQOL 12M (N=48)		Neurocognitive 12M (N=25)	
	n	%	n	%	n	%
Sex						
Male	28	53.8	27	56.3	14	56.0
Race						
White	33	70.2	33	76.7	18	81.8
African American	5	10.6	3	7.0	0	0.0
Other	3	6.4	2	4.7	0	0.0
Multiple races	6	12.8	5	11.6	4	18.2
Race unknown	5	9.6	5	10.4	3	12.0
Hispanic						
Yes	10	20.0	10	21.7	3	13.0
Ethnicity missing	2	3.8	2	4.2	2	8.0
Highest household education						
High school graduate or less	9	21.9	12	25.5	5	20.0
Some college or more	32	78.1	35	74.5	20	80.0
Education missing	11	21.2	1	2.08	0	0.0
Number of parents in household						
1	13	25.0	12	25.0	4	16.0
2	39	75.0	36	75.0	21	84.0
Age at PALF presentation						
(< 4 years)	18	34.6	21	43.8	7	28.0
(4 years, <13 years)	12	23.1	10	20.8	9	36.0
(13 years, <18 years)	22	42.3	17	35.4	9	36.0
Age at survey completion						
(1 month, < 3 years)	6	11.5	5	10.4	0	0.0
(3 years, < 6 years)	17	32.7	19	39.6	10	40.0

Characteristic	HRQOL 6M (N=52)		HRQOL 12M (N=48)		Neurocognitive 12M (N=25)	
	n	%	n	%	n	%
(6 years, < 18 years)	28	53.8	22	45.8	15	60.0
18 years or older	1	1.9	2	4.2	0	0.0
Final Diagnosis						
Indeterminate	24	46.2	23	47.9	11	44.0
Acetaminophen overdose	10	19.2	5	10.4	3	12.0
Autoimmune marker positive	6	11.5	7	14.6	4	16.0
Metabolic disorder	1	1.9	3	6.3	1	4.0
Viral infection	0	0	0	0	0	0
Other specified diagnosis	11	21.2	10	20.8	6	24.0
Maximum Hepatic Encephalopathy Level*						
Grade 0	22	42.3	17	35.4	8	32.0
Grade I	12	23.1	11	22.9	6	24.0
Grade II	9	17.3	10	20.8	4	16.0
Grade III	6	11.5	7	14.6	4	16.0
Grade IV	3	5.8	3	6.3	3	12.0
Intubation	11	21.2	9	18.8	6	24.0
Dialysis	3	5.8	1	2.1	1	4.0
Liver Transplant	24	46.2	24	50.0	13	52.0

* Initial hospitalization through follow-up

Behavior Rating Inventory of Executive Function (BRIEF)

Table 2

PedsQL™ Generic Core Scales Scores for Pediatric Patients with Acute Liver Failure at 6 and 12 Months after PALF presentation versus Healthy Controls

Generic Core Scales	PALF 6M FU ^a	PALF 12M FU ^b	Healthy Controls ^c	Differences a vs. c (adj. p-value)	Differences b vs. c (adj. p-value)	Effect Size a vs. c	Effect Size b vs. c
	Mean (SD)	Mean (SD)	Mean (SD)				
Child Self-Report	N = 30	N = 25	N = 828				
Total Score	76.38 (17.73)	72.54 (16.01)	85.51 (11.61)	9.13 *** (0.0003)	12.97 *** (0.0002)	0.77	1.10
Physical Health	80.21 (17.08)	76.00 (17.06)	89.65 (11.46)	9.44 *** (0.0003)	13.65 *** (0.0002)	0.81	1.17
Psychosocial Health	74.33 (20.88)	70.53 (17.13)	83.36 (13.37)	9.03 *** (0.0003)	12.83 *** (0.0002)	0.66	0.95
Emotional Functioning	72.50 (24.45)	65.80 (23.84)	81.15 (17.64)	8.65 * (0.0200)	15.35 *** (0.0002)	0.48	0.86
Social Functioning	81.17 (21.48)	78.40 (21.10)	86.98 (15.67)	5.81 * (0.050)	8.58 ** (0.0080)	0.37	0.54
School Functioning	69.33 (26.84)	66.96 (19.41)	81.83 (15.75)	12.50 *** (0.0003)	14.87 *** (0.0002)	0.77	0.94
Parent Proxy-Report	N = 52	N = 43	N = 1038				
Total Score	77.57 (17.76)	76.65 (21.33)	85.47 (13.46)	7.90 *** (0.0003)	8.82 *** (0.0004)	0.58	0.64
Physical Health	80.69 (21.66)	78.34 (26.06)	88.43 (16.08)	7.74 ** (0.0020)	10.09 *** (0.0004)	0.47	0.61
Psychosocial Health	75.65 (17.93)	76.26 (20.26)	83.81 (14.08)	8.16 *** (0.0003)	7.55 ** (0.0030)	0.57	0.53
Emotional Functioning	73.17 (21.49)	73.72 (21.47)	82.57 (15.68)	9.40 *** (0.0003)	8.85 *** (0.0004)	0.59	0.56
Social Functioning	82.16 (19.09)	80.48 (22.52)	87.29 (16.97)	5.13 * (0.036)	6.81 * (0.012)	0.30	0.40
School Functioning	66.95 (22.65)	72.34 (24.29)	81.09 (18.04)	14.14 *** (0.0003)	8.75 *** (0.012)	0.77	0.48

Note:

* $P < 0.05$,

** $P < 0.01$,

*** $P < 0.001$, based on independent samples t -tests (2-tailed significance, Hochberg correction for multiple comparisons).

FU = Follow up interval from baseline assessment. SD = standard deviation. Effect sizes are designated as small (0.20), medium (0.50), and large (0.80). Higher scores equal better HRQOL.

Table 3

PedsQL™ Multidimensional Fatigue Scale Scores for Pediatric Patients with Acute Liver Failure at 6 and 12 Months after PALF presentation versus Healthy Controls

Fatigue Scale	PALF 6M FU ^a	PALF 12M FU ^b	Healthy Controls ^c	Differences a vs. c (adj. p-value)	Differences b vs. c (adj. p-value)	Effect Size a vs. c	Effect Size b vs. c
	Mean (SD)	Mean (SD)	Mean (SD)				
Child Self-Report	<i>N</i> = 31	<i>N</i> = 24	<i>N</i> = 112				
Total Fatigue Score	68.41 (23.03)	64.12 (15.81)	83.13 (12.46)	14.72 *** (0.0002)	19.01 *** (0.0001)	0.96	1.45
General Fatigue	72.04 (25.91)	68.75 (19.50)	87.53 (13.22)	15.49 *** (0.0002)	18.78 *** (0.0001)	0.93	1.30
Sleep/Rest Fatigue	61.15 (24.42)	62.33 (18.49)	77.90 (16.48)	16.75 *** (0.0002)	15.57 *** (0.0001)	0.91	0.93
Cognitive Fatigue	72.04 (26.16)	61.29 (22.24)	83.97 (15.39)	11.92 ** (0.0020)	22.68 *** (0.0001)	0.66	1.35
Parent Proxy-Report	<i>N</i> = 52	<i>N</i> = 45	<i>N</i> = 148				
Total Fatigue Score	72.52 (22.05)	71.27 (20.99)	89.26 (10.28)	16.74 *** (0.0001)	17.99 *** (0.0001)	1.17	1.33
General Fatigue	72.91 (23.91)	71.85 (25.29)	90.20 (11.27)	17.29 *** (0.0001)	18.35 *** (0.0001)	1.11	1.17
Sleep/Rest Fatigue	70.03 (24.93)	72.04 (24.52)	88.92 (12.89)	18.89 *** (0.0001)	16.88 *** (0.0001)	1.12	1.03
Cognitive Fatigue	75.08 (24.88)	69.91 (25.82)	88.66 (14.90)	13.57 *** (0.0001)	18.75 *** (0.0001)	0.75	1.04

Note:

* $P < 0.05$,

** $P < 0.01$,

*** $P < 0.001$, based on independent samples *t*-tests (2-tailed significance, Hochberg correction for multiple comparisons).

FU = Follow up interval from baseline assessment. SD = standard deviation.

Effect sizes are designated as small (0.20), medium (0.50), and large (0.80).

Higher scores equal better HRQOL (less fatigue).

Table 4

Child measure of Cognitive Fatigue (n= 55 observations in 34 participants)

	Estimate	Standard Error	P-value
Intercept	80.57	11.30	<0.0001
Age at PALF presentation			0.62
< 4 Years	n/a		
4 – < 13 years	Ref		
13 – 18 years	–4.58	9.04	0.62
12 month follow-up interval (6M vs. 12M)	–11.87	4.14	0.01
Parental education > High School graduate	–9.17	9.16	0.33
Liver transplant	5.87	8.30	0.48
Intubated during the PALF event	–3.47	11.07	0.76
Maximum encephalopathy II,III, or IV	0.53	10.47	0.96

Table 5

Parent measure of Cognitive Fatigue (n= 95 measures in 60 participants)

	Estimate	Standard Error	P-value
Intercept	88.93	7.54	<0.0001
Age at PALF presentation			0.13
< 4 Years	Ref		
4 - < 13 years	-9.35	8.44	
13 – 18 years	-14.92	7.15	
12 month follow-up interval (6M vs. 12M)	-7.27	3.81	0.07
Parental education > High School graduate	-6.15	6.81	0.37
Liver transplant	4.34	6.77	0.53
Intubated during the PALF event	-0.97	8.11	0.91
Maximum encephalopathy II,II, or IV	-4.39	7.85	0.58

Behavior Rating Inventory of Executive Function (BRIEF) -parent executive functioning surveys at 6 and 12 months after PALF presentation compared to test norms.[‡]

Table 6

		6 Months				12 Months			
		Observed		Expected	Effect size Adj. p-value	Observed		Expected	Effect size Adj. p-value
		N	%	%		N	%	%	
BRIEF Preschool (2 – 5 years)		(n=14)				(n=10)			
Global Executive Composite	50 [z 0]	7	50.0	50.0	1.3 0.0017	4	40.0	50.0	1.2 0.03
	51–60 [–1 z < 0]	1	7.1	34.1		4	40.0	34.1	
	61–70 [–2 z < –1]	3	21.4	13.6		0	0.0	13.6	
	>70 [z < –2]	3	21.4	2.3		2	20.0	2.3	
Emergent Metacognition									
	50 [z 0]	6	42.9	50.0	1.7 0.0006	5	50.0	50.0	1.2 0.03
	51–60 [–1 z < 0]	3	21.4	34.1		3	30.0	34.1	
	61–70 [–2 z < –1]	1	7.1	13.6		0	0.0	13.6	
	>70 [z < –2]	4	28.6	2.3		2	20.0	2.3	
Inhibitory Self-Control									
	50 [z 0]	6	42.9	50.0	1.25 0.0032	3	30.0	50.0	0.64 0.18
	51–60 [–1 z < 0]	3	21.4	34.1		5	50.0	34.1	
	61–70 [–2 z < –1]	2	14.3	13.6		1	10.0	13.6	
	>70 [z < –2]	3	21.4	2.3		1	10.0	2.3	
Flexibility Index									
	50 [z 0]	8	57.1	50.0	1.79 0.0001	5	50.0	50.0	0.78 0.16
	51–60 [–1 z < 0]	0	0.0	34.1		1	10.0	34.1	
	61–70 [–2 z < –1]	2	14.3	13.6		3	30.0	13.6	
BRIEF School Age (6 years)		(n = 17)				(n = 16)			
Global Executive Composite	50 [z 0]	8	47.1	50.0	0.27 0.77	6	37.5	50.0	0.54 0.33
	51–60 [–1 z < 0]	5	29.4	34.1		5	31.3	34.1	

		6 Months				12 Months			
		Observed		Expected	Effect size Adj. p-value	Observed		Expected	Effect size Adj. p-value
		N	%	%		N	%	%	
		3	17.6	13.6		5	31.3	13.6	
	61–70 [–2 z < –1]								
	>70 [z < –2]	1	5.9	2.3		0	0.0	2.3	
Behavioral Regulation Index									
					0.62 0.20				0.78 0.06
	50 [z 0]	8	47.1	50.0		5	31.3	50.0	
	51–60 [–1 z < 0]	5	29.4	34.1		8	50.0	34.1	
	61–70 [–2 z < –1]	2	11.8	13.6		1	6.3	13.6	
	>70 [z < –2]	2	11.8	2.3		2	12.5	2.3	
Metacognition Index									
					0.64 0.20				0.44 0.33
	50 [z 0]	9	52.9	50.0		9	56.3	50.0	
	51–60 [–1 z < 0]	4	23.5	34.1		3	18.8	34.1	
	61–70 [–2 z < –1]	2	11.8	13.6		4	25.0	13.6	
	>70 [z < –2]	2	11.8	2.3		0	0.0	2.3	

‡ Test norms: mean $\pm$ SD = 50 $\pm$ 10 (higher score is worse)

Neurocognitive performance of participants at 12 months after PALF presentation compared to test norms (ages 3 – 16 yrs old combined)

Table 7

	N	Mean	SD	Comparison to normal Nominal p-value	Adjusted Significance Level (Hochberg)
WISC-IV/WPPSI-IV [‡]	25				
Full Scale IQ	25	95.56	15.62	0.094	0.25
Verbal Comprehension Index	25	98.00	17.26	0.25	0.25
Perceptual Reasoning Index / Visual Spatial Index	25	91.76	14.42	0.021	0.126
Working Memory Index	25	99.48	18.47	0.25	0.25
Processing Speed Index (age 4+)	22	93.95	13.85	0.119	0.25
Cognitive Proficiency Index	22	94.91	17.20	0.25	0.25
Fluid Reasoning Index (age 4–7 only; older WPPSI-IV)	9	91.44	11.57	0.192	--
ABAS-II [‡]					
Global Adaptive Composite	22	100.55	15.77	0.25	
VMI [‡]					
Visual Motor Integration	25	90.28	13.83	<0.001	0.0002
Visual Perception	25	95.48	17.78	0.114	0.114
Motor Coordination	25	85.08	15.20	<0.001	0.0002
CPT-II/K-CPT [‡]					
Omission Errors	19	47.69	7.40	0.213	0.25
Commission Errors	19	53.21	11.43	0.25	0.25
Hit Reaction Time	19	47.45	11.27	0.072	0.25
RT Standard Error	19	49.92	8.76	0.25	0.25
Variability	19	50.80	10.71	0.25	0.25
Detectability	19	53.29	12.16	0.063	0.25

[‡]Test norms: mean±SD = 100±15

[‡]Test norms: mean±SD = 50±10 (higher score is worse)

Wechsler Intelligence Scales for Children-4th edition (WISC-IV)

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- Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV)
- Adaptive Behavior Assessment System-Second Edition (ABAS-II)
- Beery-Buktenica Developmental test of Visual-Motor Integration, 6th Edition (VMI-6)
- Conners' Continuous Performance Test II (CPT-II)
- Conners' Kiddie Continuous Performance Test (K-CPT)

Table 8

Univariate analysis for Beery-Buktenica Developmental test of Visual-Motor Integration, 6th Edition (VMI-6) Motor Coordination score (n = 25; ages 3–16)

Motor Coordination Score	Motor Score [‡] mean±SD	t-statistic	p-value for t-statistic
Liver Transplantation		−1.03	0.31
Yes (n= 13)	88.1 ± 16.0		
No (n = 12)	81.8 ± 14.2		
Highest Parental Education		−1.07	0.30
High School (n= 5)	78.6 ± 19.0		
> High School (n = 20)	86.7 ± 14.2		
Encephalopathy – Baseline at PALF presentation		0.37	0.72
0,I (n = 19)	87.2 ± 14.2		
II,III,IV (n = 3)	84.0 ± 9.6		
Encephalopathy – Peak during hospitalization		0.60	0.56
0,I (n = 14)	86.7 ± 15.2		
II,III, IV (n=11)	83.0 ± 15.7		

[‡]Test norms: mean±SD = 100±15