7 Psychosocial, Cognitive, and Quality of Life Considerations in the Child with Liver Disease and Their Family

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Introduction

Chronic liver disease (CLD) encompasses a wide variety of pathologic conditions that may present in infancy such as biliary atresia (BA), progressive familial intrahepatic cholestasis (PFIC), and metabolic syndromes or present later in life such as Wilson disease (WD) and anywhere in between such as autoimmune hepatitis.

Children with liver disease frequently have chronic morbidity necessitating frequent hospitalizations and invasive medical procedures. Unexpected complications, complex medication regimens, unpalatable dietary requirements, and uncertainty regarding outcomes are sources of mounting stress for the child and their family. Other stressors include difficulty with schoolwork due to prolonged absences and cognitive deficits, trouble concentrating, and ridicule by peers. Liver transplantation (LT), although lifesaving, can also be a distressing and challenging experience for many families.

The study of the psychosocial, cognitive, and health-related quality of life (HRQOL) outcomes of chronic liver disease and liver transplantation in children and adolescents is relatively recent. The shift from research focused on reducing mortality to investigation of functional outcomes did not occur until survival rates improved in the mid-1990s. Research efforts have been limited by the small numbers of potential participants at individual medical centers, and only recently have research groups been able to organize and fund multicenter studies to explore outcomes. Several psychosocial and cognitive analyses have been performed in small, heterogeneous, single-center samples, often including patients with broad age ranges and varied disease presentations. Further, different measures are often needed for subjects of different ages within the same sample, making

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interpretation more difficult and pre- vs. post-transplant comparisons less useful.

Qualitative analysis of the perceptions of parents of children with CLD reveals a tremendous sense of guilt, frustration regarding loss of control, fear of the future, and anxiety related to uncertainty of the child's outcomes [1]. Children with CLD also perceive their illness as being out of their control [2]. These are important considerations as youth with a chronic illness are two to four times more likely than their healthy peers to have a psychiatric diagnosis at some time during their childhood or adolescence [3].

We will briefly review the psychosocial and cognitive development as well as HRQOL of patients with liver disease and discuss changes that may occur after transplantation. Psychosocial development includes mood, behavior, and social interactions and reflects the child's ability to adjust to difficult situations such as liver disease and transplantation. Cognitive development reflects the child's ability to think, learn, concentrate, problem-solve, and communicate. HRQOL is a broad multidimensional concept that reflects an individual's total well-being including the emotional, social, and physical aspects of their life. The current body of data is limited in its utility due to reliance primarily on small, single-center samples; however, these studies represent an important first step in furthering our knowledge.

Chronic Liver Disease

Chronic liver disease is caused by a heterogeneous group of disorders that can present at any age. The developmental problems faced by an infant with end-stage liver disease secondary to biliary atresia are quite distinct from those of an adolescent with compensated cirrhosis secondary to autoimmune hepatitis. However, there are some features that are shared including the impact of repeated hospitalizations and the potential for cognitive and motor dysfunction due to minimal hepatic encephalopathy, malnutrition, and other medical factors. We will first review some of these commonalities and then detail analyses that have been performed in single-disease cohorts.

Minimal Hepatic Encephalopathy (MHE)

Cognitive Outcomes

MHE may affect children with chronic liver disease of any etiology. The signs and symptoms that may reflect early encephalopathy in children such as crying, irritability, and inattention to task are also observed in children that are moderately ill from any cause, making the diagnosis of MHE in pediatric patients, especially those who are very young, much more challenging than in adults. The consequences of long-term MHE on the developing child's brain are largely unknown. A few studies in the USA [4] and India [5–7] have examined MHE in children using magnetic resonance spectroscopy, finding significant correlations between metabolic brain function and biochemical markers of encephalopathy (plasma ammonia levels and the ratio of branched-chain to aromatic amino acids [BCAA/AAA]). Additionally, correlations between mean diffusivity on diffusion tensor imaging (DTI), plasma ammonia, and brain glutamine/glutamate levels implicate ammonia as playing a key role in the development of low-grade cerebral edema in MHE in children, as in adults [5–7]. Increased pro-inflammatory cytokines have been found in patients with MHE relative to controls, suggesting that both hyperammonemia and pro-inflammatory cytokines play a role in the development of cerebral edema associated with MHE [7]. These studies provide important clues regarding the mechanism for development of hepatic encephalopathy (HE) and a role for imaging in the diagnosis of MHE in children. Also, greater deficits in visuomotor coordination, short-term memory, and visual perception were seen in patients with MHE, and these were associated with increased mean diffusivity, indicating subclinical edema [6].

Some studies suggest that cognitive impairment may improve, especially in fluid abilities, with interventions targeting MHE. Treatment of portal hypertension [8–10] in two patients with surgical repair of congenital portal systemic shunts (PSS) resulted in improvement in

learning/memory, stamina/energy, mood, fine motor speed, reading, and IQ [8]. Improvement was reported in all 4 patients who had cognitive deficits in a retrospective review of 10 patients who had surgical repair of congenital PSS [10]. A prospective study of 12 patients who had extrahepatic portal vein thrombosis and no overt HE also found improvement in fluid abilities (attention, mental speed, and verbal memory) and motor speed/dexterity following surgical repair [9]. However, fluid abilities (executive functions) have not been found to improve universally after treatment of liver disease. In a multisite, longitudinal study of children with hepatitis C virus [11, 12], patients showed worse executive function on a parental questionnaire compared with norms even after 24 weeks of pharmacological treatment. Executive deficits have also been found to persist at least 2 years after liver transplantation [13].

Psychosocial and HRQOL Outcomes

The emotional impact of MHE in children is unknown. Studies in adults with chronic liver disease have demonstrated that MHE through its effects on executive and psychomotor function leads to inability to perform complex tasks and even premature retirement from the workforce [14]. A study of Chinese patients with MHE revealed lower scores in all domains of the Short Form 36 (SF-36) when compared to patients with chronic liver disease without MHE [15]. However, a larger prospective study of 77 patients, 29 of whom had MHE, did not reveal significant differences in HRQOL using the SF-36 [16]. These studies used different criteria for diagnosing MHE which may explain the discrepancies in their findings. With these data, we may surmise that children who typically have fewer coping skills than adults may be at higher risk of developing emotional, behavioral, and social problems as well as lower HRQOL related to MHE. Older children with MHE, specifically those in demanding academic environments, may have difficulty keeping up with their peers, which will also affect their HRQOL.

Cirrhosis

Psychosocial and HRQOL Outcomes

Overall, most children with CLD are well adjusted compared to their peers but feel less in control due to their illness [2]. Children with cirrhosis have changes in their energy levels and appearance that may adversely affect regular social interactions. Reports from the late 1980s found that children with liver disease had moderate to severe deficits in social functioning prior to LT as measured by the Child Behavior Checklist (CBCL) and the Minnesota Child Development Inventory (MCDI) [17, 18]. In a more recent study, parents also reported social deficits in children with less advanced liver disease, suggesting that alterations in peer relationships may be an early feature. Disease severity in that study did not correlate with the level of social functioning. Instead, increased family cohesion, as measured by the Family Adaptability and Cohesion Evaluation Scales (FACES-III), was a marker for better social adaptation even though these children scored significantly lower when compared to a normative sample of healthy children [19].

Patients with chronic liver disease are expected to have lower quality of life as compared to a normative population, especially in the physical domain. Assessment of HRQOL in pediatric patients with cirrhosis has not kept pace with that of liver transplant recipients and studies that assess HRQOL before and after transplant are rare. An important obstacle in this area is that many CLD patients present in infancy or early childhood and the lack of HRQOL assessment scales for these age groups has made measuring functional status and improvements in quality of life difficult. Development of newer tools specifically designed for infants may improve our ability to target this population [20]. One study of infant transplant candidates measured HRQOL at listing for transplant and at 6- and 12-month follow-up after transplant, using the Infant Toddler Health Status Questionnaire (ITHQ). Scores were significantly improved after transplant across multiple domains, with the largest improvements seen in Global Health, Growth and Development, Discomfort and Pain, and Parental Emotional Impact [21].

Biliary Atresia

Cognitive Outcomes

In the few studies that have been performed in children with biliary atresia (BA) surviving with their native liver, IQ and developmental functioning ranges from borderline to average. Early disease onset (age 0–5), diminishing liver function, and growth failure (especially in younger children) have been highlighted as important correlates of intellectual deficits. In an early landmark study, overall cognitive functioning on the Bayley or Stanford-Binet L-M fell in the borderline range (infants M = 79.5; children M = 76.1) with extremely low motor skills (infants M = 69.7; children M = 56.9). Infants' mental and motor developments were associated with growth parameters, whereas children's development was more closely associated with liver function [22]. The most recent study of very young BA patients mirrored earlier findings of very significant delays especially in motor skills (M = 71.8) and expressive language (79.9) on the Mullen Scales associated with liver function, growth parameters, and age at Kasai procedure (the earlier the better) [23].

Similarly, in more heterogeneous samples of patients with end-stage liver disease (ESLD), those with early disease onset (<1 year) had lower IQ than those with later onset (early M = 85.0 vs. late M = 99.5) [24]. Worse outcomes were related to longer illness duration, poorer nutritional status, and vitamin E deficiency. In a subsequent study [25], lower IQ was also found in early- vs. late-onset patients, although late-onset patients scored lower than test norms only on verbal IQ on the Wechsler Intelligence Scale for Children-Revised (WISC-R). IQ was best predicted by liver function and duration of disease, suggesting that patients with the highest risk for poor cognitive outcomes are those with onset of liver disease in the first year of life.

Psychosocial and HRQOL Outcomes

There are likewise few studies focusing on the emotional well-being of non-transplanted survivors of biliary atresia. One report compared long-term survivors in the UK and Japan to healthy controls using the SF-36 and found that Japanese patients reported significantly lower scores in emotional and social functioning compared to their peers in the UK. However, the overall numbers were small (21 vs. 25 patients) [26]. Prior to LT, children are noted to be overly dependent and demanding, and as with all patients with cirrhosis, physical appearance and energy levels restrict physical activity and social interactions [18].

Inherited Cholestatic Diseases

Cognitive Outcomes

Original descriptions of patients with Alagille syndrome described cognitive delay as an important feature. However, it now appears more likely that cognitive delay in these early reports may have been related to prolonged hospitalization, malnutrition, and especially fat-soluble vitamin deficiencies [27, 28]. Improvements in nutritional management may have resulted in fewer reports of associated developmental delay. There is a single case report of a 16-year-old with progressive familial intrahepatic cholestasis (PFIC) whose symptoms included apathy, cognitive impairment, and extrapyramidal syndrome [29]. However, there are no studies that systematically address cognitive outcomes in children with PFIC prior to transplantation. Assessment of these outcomes in this and other rare forms of childhood liver disease has been a priority for the Childhood Liver Disease Research and Education Network (ChiLDREN http://childrennetwork.org), and thus these data should be forthcoming.

Psychosocial and HRQOL Outcomes

One report of HRQOL in 71 patients with Alagille syndrome revealed lower HRQOL for both psychosocial and physical function as compared to the general population; see Fig. 7.1. Cardiac catheterization or surgery, mental health diagnosis, and poor sleep were associated with lower HRQOL in this cohort [30].

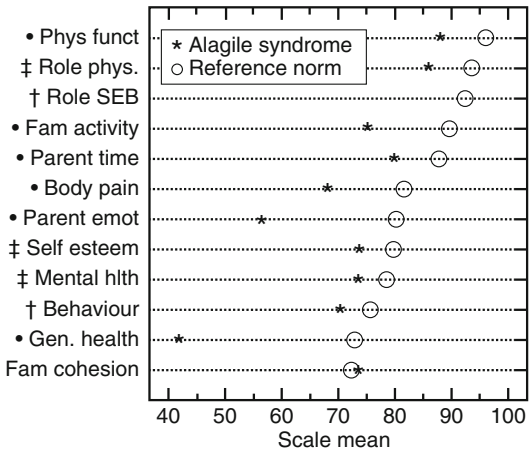

Fig. 7.1 Mean CHQ subscale scores for Alagille syndrome and the normative population and differences between the cohorts. Difference between cohorts: † $p<0.05$, ‡ $p<0.01$, *stands for a p<0.005. (Reproduced with permission from Elisofon et al. [30])

Wilson Disease (WD)

Cognitive Outcomes

WD can present with progressively worsening symptoms that are not diagnosed for months or years or with acute decompensation of neurological, psychiatric, and/or liver functioning. Thus, outcomes may be quite variable, in part related to the progression of the disease prior to treatment initiation, the stage of treatment, and the type of symptoms at presentation. A retrospective review of WD patients ($n=129$) suggested a pattern of early improvement following treatment, in both hepatic and neuropsychiatric symptoms with a subsequent plateau in these symptoms [31]. However, two smaller studies ($n<10$) did not show significant neurological improvement or change in IQ with therapy [32, 33]. Imaging studies suggest that patients with WD have cognitive deficits in areas such as processing speed, executive functioning, attention, learning/memory, visuoconstructive ability, and verbal fluency that appear to be associated with brain abnormalities in basal ganglia, brainstem, thalamus, frontal lobes, and general cognitive atrophy [34, 35].

Psychosocial and HRQOL Outcomes

There are limited studies assessing the emotional health of children with WD. This may be due to the focus on and difficulty differentiating between neurological symptoms and emotional disorders. In fact, patients with primarily neurological or psychiatric symptoms (such as personality change) are typically diagnosed later than those with primarily hepatic symptoms and may actually be misdiagnosed initially, leading to more disease progression prior to treatment [36]. Case reports detail hyperactivity, poor sleep, and bad temper in undiagnosed children with WD that improve after therapy [37]. A small study ($n=23$) of adults with WD found they had an increased prevalence of major depressive disorders as well as bipolar disorder [38].

Svetel et al. [39] conducted a cross-sectional study to identify clinical and demographic factors influencing health-related quality of life in 60 treated, clinically stable patients with WD using the SF-36. The level of disability and grading of WD severity were assessed by the Global Assessment Scale for WD [GAS for WD]; cognitive impairment and depressive features were assessed respectively by the Mini Mental State Examination [MMSE] and the 21-item Hamilton Depression Rating Scale [HDRS]. Lower scores on the SF-36 domains were found in patients with neurological and psychiatric symptoms compared with those with a predominantly hepatic form of WD. SF-36 scores were also lower in those who were depressed, who had cognitive impairment, and had a longer latency from appearance of symptoms to treatment initiation.

Metabolic Liver Disease

Cognitive Outcomes

Outcomes vary widely depending on the disease presentation. Certain disorders such as urea cycle defects (UCD) and tyrosinemia present in early infancy with severe hyperammonemia that may result in profound brain damage. Thimm et al. assessed the cognitive and motor fdevelopment

of nine patients who ranged in age from 1 to 8.5 years with tyrosinemia type I using the Bayley Scales, Snijders-Oomen test, Kaufman Assessment Battery for Children (KABC), and Movement Assessment Battery for Children. Six of the nine patients tested below normal with one patient testing in the mild to moderate mental disability range. Four of seven patients tested for motor abilities also scored below the normal range [40]. Krivitzky et al. in an analysis of 92 patients with UCD reported 30 % of patients as having intellectual disabilities with a greater proportion of those affected having neonatal onset of disease. The number of hyperammonemic episodes was not a significant factor in IQ levels in these subjects. All patients had difficulties in social interactions, attention deficit, and executive functioning [41]. A report of 28 patients with ornithine carbamoyltransferase deficiency (OTC), the most common UCD, revealed 18 with disabling neurological conditions including seven with focal neurological deficits [42]. In a report assessing the effects of early vs. late transplantation in five patients with UCDs, all the children had below average developmental scores on Griffiths scales. Three of the five patients improved after transplant; however, they remained greater than one standard deviation below normal [43]. A review of 88 patients with urea cycle defects reveals that neonatal screening has improved survival; however, 2/3 continue to suffer severe neurological damage [44].

Psychosocial and HRQOL Outcomes

It appears that metabolic disorders in particular exact a very high emotional toll on the family. A survey of parents of children with urea cycle defects reported that almost half thought of their children dying every day and a quarter of parents did not feel they could change jobs due to insurance [45].

Mitochondrial disorders frequently present with liver failure but also can cause chronic liver disease. The majority of these patients are not transplant candidates because they suffer from progressive neurologic injury as well and succumb to these complications even following successful transplantation [46]. However, there are a small number of these disorders that are associated with more chronic neurological injury which is not life-limiting. Isolated case reports of these survivors do not detail cognitive status or functional outcomes, and the rarity of these patients limits accumulated experience [47].

Hepatitis C Virus

Cognitive Outcomes

Hepatitis C virus (HCV) is generally considered to be asymptomatic in childhood; however, in a study of treatment-naïve patients ($n = 114$) using the Behavior Rating Inventory of Executive Function (BRIEF), 18 % had clinically significant impairment in executive function, including working memory. However, overall they performed better than children with attention-deficit/hyperactivity disorder (ADHD) [11]. Adults with HCV also have decreased cognitive [48] and psychological functioning [49].

Psychosocial and HRQOL Outcomes

Once therapy is initiated, the use of interferon alfa, which remains the standard of care, increases the risk of psychiatric disorders such as depression and anxiety [49]. Although the use of newer agents such as protease inhibitors has led to promising outcomes, unless treatment strategies change, it is likely that children who are infected with HCV today will face these same side effects when they are treated in adulthood. In the absence of functional impairment, children and adolescents may not experience any behavioral or emotional sequelae that may be linked to their medical diagnosis [12]. This perception of well-being seems to negate parental concern of future morbidity and has led to a lack of services to provide support for these families.

Hepatitis C is considered to have an asymptomatic course in early childhood. HCV, especially in the early stages, may not cause any significant impairment in physical functioning, social activities, and bodily discomfort. However, Nydegger et al. using the Child Health Questionnaire (CHQ) have reported marked reductions in emotional, general health, parent

impact-emotional, and time scores. Children self-reported scores comparable to their healthy peers with the exception of lower scores in physical functioning. While 73 % of parents reported being worried "a lot" about their child's future health, only 10 % of children were concerned about being treated differently or about the risk of future medical complications such as liver cancer [50]. In a study of 114 treatment naïve children with HCV, parents reported significant emotional impact from their child's illness as well as a perception that they were less healthy on the CHQ. Family activities and cohesion were unaffected as was mental health and self-esteem. Mothers who transmitted the disease to their child reported lower emotional scores on the SF-36 compared to parents who did not transmit the virus. Good caregiver emotional and mental health was associated with patient psychosocial health with only two children scoring in the depressed range on the Childhood Depression Inventory [11].

Liver Transplantation

Liver transplant recipients now enjoy survival rates exceeding 85 % at 5 years [51]. Although "cured" of their underlying disease, these patients continue to face the long-term effects of chronic immunosuppression, fear of graft failure, and the need for lifelong medical surveillance.

Cognitive Outcomes

Studies examining post-LT cognitive functioning over the past decade have mostly reinforced earlier findings. IQ is nearly universally below published norms [13, 52–55]. Pediatric LT patients clearly have a downward shift in IQ, with mean IQ scores typically in the mid-80s to low-90s and an increased prevalence (up to 27 % vs. 2 % expected) of scores falling below 70 [13, 52, 56, 57]. One study of long-term LT survivors aged 3–9 years revealed that almost 20 % had an IQ of less than 70 [58]. Patients who experience liver disease earlier in life appear to be at higher risk for developmental delay which may be further exacerbated during the transplant process. An analysis of 40 infants with biliary atresia who were assessed before transplant and again 3 and 12 months after transplant revealed that mean Bayley scores for both mental and psychomotor development, which were in the low average range, dropped by another standard deviation at 3 months following transplant. One year after transplant 35 % were diagnosed as developmentally delayed and mean scores had improved only to the pre-transplant level. Delayed development was associated with decreased weight at transplant, low albumin, length of hospital stay, and younger age at transplant [59].

Studies of cognitive outcomes following LT have primarily focused on IQ, and therefore, less is known about other cognitive domains. Most have found similarly delayed verbal and nonverbal IQ [13, 52, 57]. However, one study [56] found significantly weaker language processing on the Clinical Evaluation of Language Fundamentals-Preschool or Revised (CELF-P/CELF-R) compared with controls with cystic fibrosis. Only two other studies of children with liver disease have suggested a relative weakness in language: in children under age 2 with a large proportion of non-English speakers [23] and in a retrospective review [25].

In contrast, a recent study ($n=18$; age 7–16) [60] reported poorer nonverbal IQ ($M=88.9$), but not verbal IQ ($M=99.6$) or full scale IQ (94.0) compared with WISC-III norms. This study also found poorer performance on visuospatial, visuoconstructive, and social perception tasks on the NEPSY-II, but not in language, attention/executive function, or memory and learning. Other studies have reported deficits in visuomotor skills ($M=82$) [57] and lower nonverbal IQ ($M=84.5$) than verbal IQ ($M=90.6$) in 30 % of patients on the Wechsler scales [52]. Such findings are in line with prior report by the Stewart group [61] and recent report of MHE outcomes [6].

The few pediatric studies of attention and executive functioning post-LT have typically found deficits. Several studies using the KABC have found deficits in both sequential (i.e., working memory) and simultaneous (i.e.,

nonverbal reasoning) performance relative to norms [53–55]. In a recent study by the same group ($n=137$; age 6–18 years), LT patients demonstrated poorer attention compared with norms in alertness, working memory, sustained attention, and divided attention [62]. A large multicenter study ($n=144$) [13] reported significant executive deficits relative to norms on the BRIEF, particularly by teacher report (Global Executive Composite = 58) (Fig. 7.2). Consistent with earlier findings by Stewart and colleagues, recent studies have also documented significant problems with learning and school functioning. Achievement was found to be below norms in several studies [13, 53, 57], but not different as compared to controls with cystic fibrosis [56]. Sorensen et al. [13] found that young LT patients demonstrated school readiness concepts consistent with peers on the Bracken Basic Concept Scale, Revised, but differed from norms in both word reading ($M=92.7$) and math ($M=93.1$) on the Wide Range Achievement Test, 4th edition.

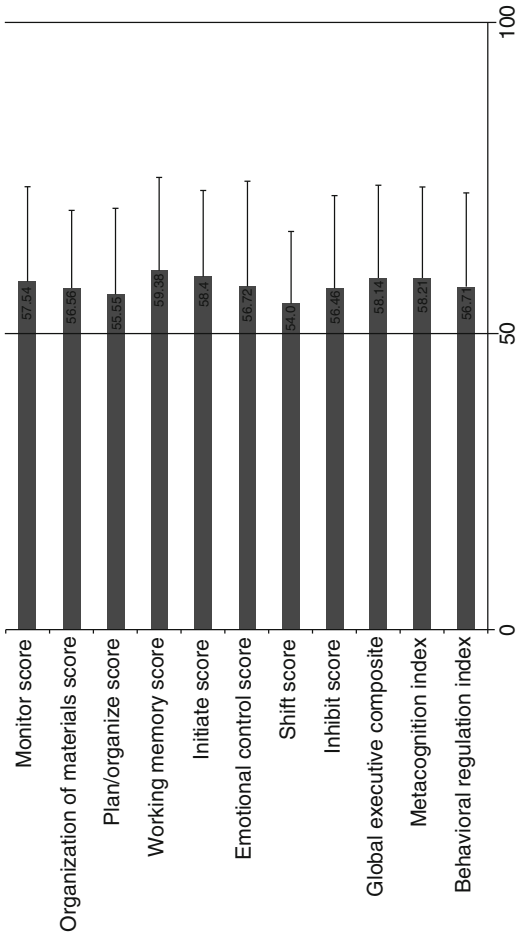

Fig. 7.2 All teacher BRIEF T scores for the pediatric liver transplant sample ($n=72$) were significantly different from the normative population ($p<0.005$). The normative population for the BRIEF has a mean T score of 50 and a standard deviation of 10, with higher scores reflecting poorer executive functioning. The Hochberg adjustment was used to control for multiple comparisons (Data from Sorensen et al. [13])

In the largest study of academic outcomes to date in pediatric LT patients ($n=823$; age 6–18) [63], 34 % of patients were receiving special education services, 11 % had received accommodations, and 20 % had repeated a grade by parent report. Diagnosis of learning disability was reported in 17.4 % and mental retardation in 5.2 %. The other large multicenter study of pediatric LT patients [13] similarly reported that 31 % had received special education in the past year and 25 % had profiles suggesting learning disability. These results are consistent with earlier findings despite substantial improvement in post-transplant survival and management over the past 15 years [58].

While recent studies have examined predictors of cognitive and academic outcomes after LT in children, the results remain mixed. Younger age at LT was found to be an important factor leading to poorer outcomes in one study [56], but not in another [53]. A retrospective review ($n=40$; age less than 6 months at LT) found "long-term" outcomes of "regular mental development" in only 28 % of participants [64]. In contrast, another study reported that younger age at transplant predicted *better* performance, but only for nonverbal IQ and achievement, not for working memory on the KABC [54].

Although one study did not find a significant effect of diagnosis or time since transplant [52], LT patients with BA performed better than those with other diagnoses in another [57]. A large study found worse attention/executive function in patients with "diagnoses affecting the brain" (Crigler-Najjar, citrullinemia, Alagille, metabolic disorders, WD, tyrosinemia) compared

with those who had diagnoses that presumably do not directly affect the brain (BA, α_1-AT, oxalosis, cholestasis, autoimmune hepatitis, liver tumor) [62]. It should be noted that this distinction is debatable.

In a moderately large sample ($n=44$), longer duration of illness and height deficient at LT predicted nonverbal IQ and achievement [54]. Another study found that 45 % of variance in nonverbal IQ was explained by growth deficits pre-LT and elevated serum ammonia, while 23 % of variance in verbal IQ was due to elevated calcineurin inhibitor levels [57]. Language deficits have been found to be associated with disease severity and peri- and post-LT complications as reflected in more days in intensive care, more days in the hospital post-LT, and elevated bilirubin pre-LT [56].

In a large multicenter school outcomes study [63], the strongest predictor of special education was pre-LT special education (odds ratio 22.5). Posttransplant factors were also predictive, including type of immunosuppression (cyclosporine or other was worse than tacrolimus) and cytomegalovirus post-LT. In a smaller study ($n=29$), age (younger better) and more normal height at LT explained 66 % of variance in achievement [53]. Slow reaction time and poor sustained attention were predicted by type of LT (deceased donor), longer duration of disease, older age at LT, and gender, although the amount of variance explained was modest (14–25 %) [62].

Consistent with previous literature, recent evidence suggests that progressive cognitive decline may be halted or even reversed after LT. A case series of patients with Crigler-Najjar syndrome type 1 suggested that earlier LT (i.e., prior to brain injury) results in better outcome [65]. A 4-year-old without brain injury remained cognitively intact post-LT, whereas children aged 7 and 12 years who had mild to moderate deficits pre-LT improved incompletely following LT. Similarly, a small series ($n=14$) of patients with maple syrup urine disease (MSUD) showed stable IQ in 57 % and improved IQ in 36 % post-LT [66]. Cognitive functioning in another metabolic disorder, propionic acidemia, also stabilized or improved post-LT according to a retrospective review ($n=12$) [67]. Stable or improved functioning up to 15 years post-LT in WD patients has also been reported ($n=32$; age 6–40) [68].

Other ESLD and BA groups were found to demonstrate stable functioning post-LT vs. pre-LT. A follow-up to an earlier report [69] on 25 infants (<1 year) undergoing LT found a slight dip in some areas of cognitive functioning on the Griffiths initially but a return to pre-LT levels by 4 years post-LT [70]. One case report suggested improved cognitive and/or academic functioning post-LT in a child with BA [71]. The child's school functioning was reduced relative to her healthy identical twin by the 2nd year of school, but following LT in middle school, her performance steadily and dramatically improved until she was performing at the level of her twin in the 3rd year of high school.

Data on cognitive outcomes and predictors in pediatric LT recipients are mixed. IQ is most clearly skewed lower than normal, although there is some evidence for deficits in other cognitive domains such as attention/executive function, learning/memory, visuospatial/nonverbal abilities, language, as well as academic functioning. Certain factors such as age at transplant have been both positively and negatively associated with improved cognitive outcomes. Other factors relating to pre-transplant disease (e.g., disease type, deficient growth, liver function, HE) as well as peri-/posttransplant issues (e.g., immunosuppressants, infection, transplant complications) may also play a role. Children with metabolic diseases may have worse outcomes when compared to those with biliary atresia; however, LT may prevent further neurological decline. The heterogeneous patient population with respect to disease category and age, as well as typically small samples, makes comparisons between studies difficult. LT recipients struggle with various neurologic deficits and further research is needed to identify factors to improve their cognitive outcomes. Additional details on cognitive outcomes in pediatric patients with liver disease and transplantation can be found in a recent review by Sorensen [72].

Psychosocial and HRQOL Outcomes

The very first studies of behavioral outcomes following LT suggested that 50 % of children show maladaptive behavior, such as temper tantrums, impulsiveness, poor concentration, defiance, and aggressive behavior [18, 73]. Furthermore, adolescents have been noted to have attention and conduct problems, particularly boys [74]. Behavioral problems rarely present in the early post-LT period, more typically manifesting in the later post-LT period, especially in those transplanted at an early age [74]. More recently, two studies demonstrated that between 1/3 and 1/2 of transplant recipients assessed with the CBCL scored in the pathological range for total problems. The most affected problem scales included withdrawal, thought problems, aggressive behavior, and attention problems [55, 75].

LT is a stressful experience for many children. However, by 5 years post-LT, children often have better emotional adjustment, compared to those with other chronic illnesses [76, 77]. In a large single-center study of 51 patients with a median time since transplant of over 10 years, parents regarded their children as having psychological health that was comparative to a normal population using the CHQ [78]. However, other studies show that transplant recipients continue to lag behind their healthy peers, with 55 % thought to have some emotional problems [52]. Parents self-report higher levels of psychological symptoms pre- and posttransplant with fathers showing greater distress than mothers [79]. Post-traumatic stress disorder (PTSD) has also been demonstrated in 16 % of adolescent patients that receive transplantation [80] and 27 % of parents of childhood LT recipients [81].

Several studies have explored the impact of liver transplantation on the parents and family. Using the Family Environment Scale, Fredericks et al. did not find a difference in cohesion among family members of transplant patients but did find higher levels of parental stress and total difficulty on the CHQ [82]. This is significant as an older study reported that more than a third of divorced or separated parents of pediatric transplant patients claimed the stress of raising a chronically ill child contributed to marital discord [18]. A recent study using the Family Assessment Device revealed similar levels of family dysfunction as a reference sample [83]. Analysis of risk factors associated with lower reported family function identified demographic factors, such as lower parental education level, and medical complications related to biliary tract obstruction as potentially important determinants of this outcome. The daily adjustments required to accommodate a child posttransplantation have also been associated with maternal depression and anxiety [84]. Given the previous research detailing altered functioning of families of children with chronic illness or disability [85], the extent to which families modify or adjust routines to accommodate children following transplantation warrants further investigation.

The largest study on school outcomes consisting of 823 children in the Studies of Pediatric Liver Transplantation (SPLIT) registry has shown that 96 % of children are able to attend school, although a significant number require special education [63]. In addition to cognitive deficits, missed school days may also contribute to compromised academic functioning. Data from the SPLIT network suggests that 30–40 % of patients in long-term follow-up miss more than 10 days of school per year, with teens having the highest rate of absences. There are conflicting reports in the literature regarding participation in extracurricular activities, with some studies reporting that the majority of children participate in organized sport and integrate well in school [86], while others suggest that social functioning and participation in activities is reduced [87]. Physical abilities measured by physical summary scores of the PedsQL™ are reduced and may contribute to less physical interaction [88].

Research focused on individual aspects of psychosocial functioning indicates some positive outcomes for children after LT such as improved attendance at school and increases in social activity and the ability to cope with everyday stress. However, there is also evidence suggesting that children continue to have psychosocial difficulties such as behavioral problems, depression, anxiety, and reduced self-esteem [55]. The risk factors for psychosocial problems post-LT remain poorly understood. Furthermore, adolescents are underrepresented in many of the studies and may present particular vulnerability or treatment challenges.

Pediatric liver transplant recipients have significantly lower HRQOL compared to healthy

controls [89–91]. The SPLIT Functional Outcomes Group (FOG) conducted a large cross-sectional analysis of generic HRQOL in 873 (363 self-report) pediatric LT recipients between the ages of 2 and 18 years using the PedsQL™ (Mapi Research Institute, Lyon, France) generic core scales. Patients in the sample had a mean age of 8.2 ± 4.4 years and 55 % were female. The median interval from transplant to survey was 3.1 years. Outcomes were compared to a sample of healthy children randomly matched by age group, gender, and race/ethnicity; see Fig. 7.3. The physical and psychosocial functioning of the LT recipients compared favorably with children with other

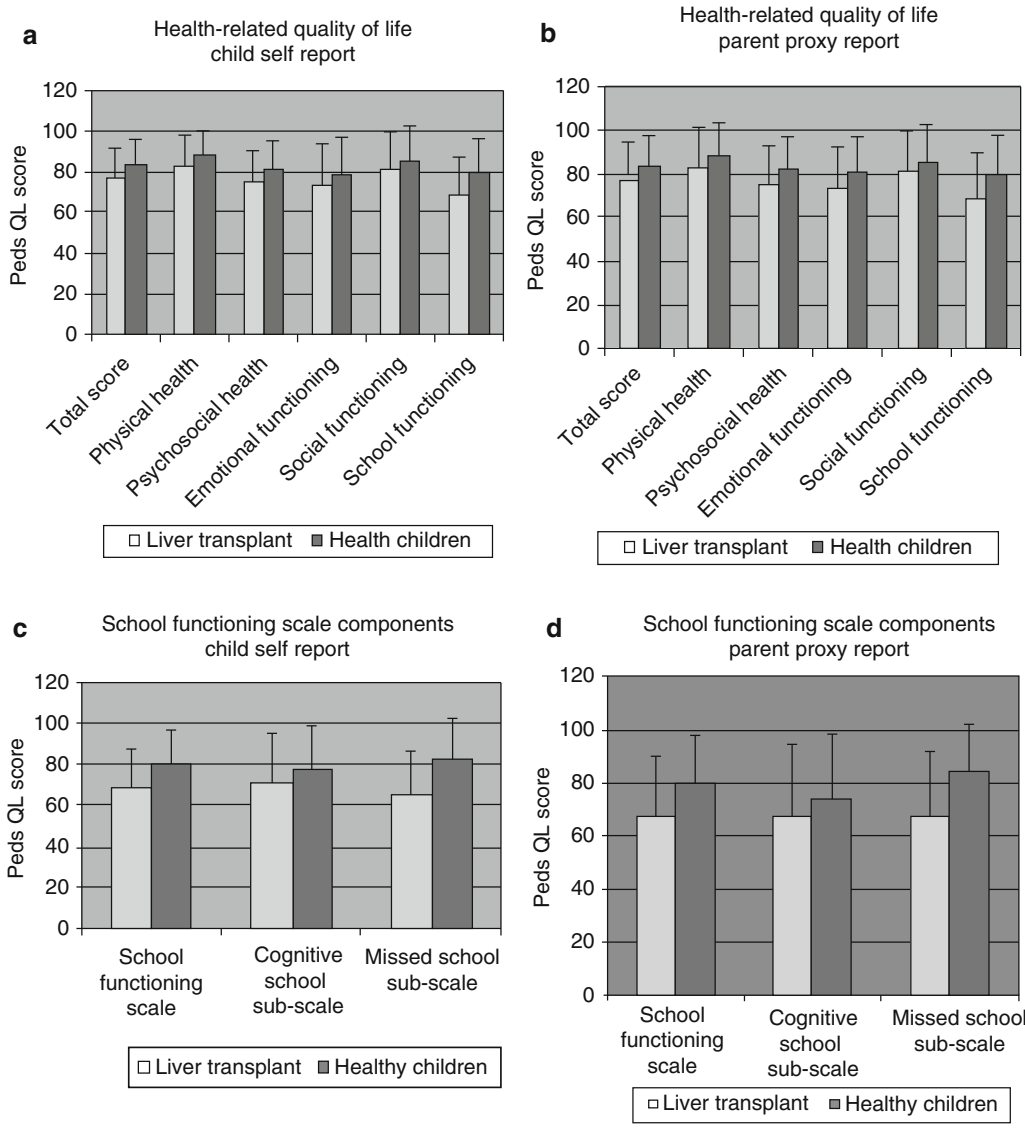

Fig. 7.3 (**a–d**) Using the PedsQL generic core scales to assess quality of life in liver transplant recipients compared to a healthy sample matched for gender, race, and age. (**a**) Patient self-report ($n = 363$) patients report significantly lower scores when compared to healthy controls. (**b**) Parent proxy report ($n = 869$) parents report lower scores compared to healthy controls. (**c**) School functioning scale by patient self-report ($n = 361$) parents of liver transplant recipients report significantly lower scores than parents of healthy children with an effect size of 0.68. (**d**) School functioning scale parent proxy report ($n = 746$) parents of liver transplant recipients report significantly lower scores than parents of healthy children (Reproduced with permission from [96])

chronic pediatric illnesses but was not equal to the healthy sample. The total scale score and subscales of the PedsQL™ 4.0 generic core scales were all significantly lower than those of healthy children ($p<0.001$) with effect sizes ranging from 0.25, for self-reported emotional functioning, to 0.68 for self-reported school functioning [89, 90]. Effect sizes greater than 0.5 are considered moderate with those approaching 0.8 considered large. The altered school functioning that is observed in this group may be secondary to an increased prevalence of cognitive deficits and learning disabilities.

Demographic as well as medical variables may predict levels of HRQOL in this population [21, 91, 92]. The impact of age on HRQOL in pediatric LT recipients has been considered in several studies. In a small, multicenter report, younger survivors (less than age 5 years) had physical and psychosocial health that was comparable to age-matched controls and higher than what was reported for older children in the same study. The SPLIT/FOG cross-sectional data set was analyzed to examine the impact of age at testing on parent report of HRQOL. Results suggest that age at testing may indeed have an important impact on HRQOL with younger children having the highest scores (Table 7.1). In fact, the impact of age at testing appears to be more significant than interval from transplant. Initial results from multivariate analysis examining the impact of various factors on parent reported HRQOL in the SPLIT/FOG study identified single-parent household, length of initial hospitalization after transplant, older age, history of seizures, lower height z score at transplant, and days hospitalized in recent follow-up as negative predictors. A large multicenter report demonstrated strong correlation between impaired cognitive functioning and lower HRQOL [93]. Additionally, the relationship between the patient's HRQOL and family dynamics bears further consideration. Studies that have included assessment of the impact of the child's health state on the parents have shown a considerable negative influence on parental emotional state and family life [52, 78, 83].

However, when formally measured, family function was found to be equal to that reported by a reference population [83]. These preliminary results suggest that services that support the parent's ability to cope with their child's health condition would likely improve the child's HRQOL. This strategy is especially important as the patients' level of HRQOL has been linked to adherence behaviors and possibly maintenance of graft function [94].

Implications for Practice and Research Opportunities

As the number of patients surviving pediatric liver disease/LT increases, many questions with regards to the long-term psychosocial, cognitive, and HRQOL outcomes remain unanswered. Appropriate interventions for the abnormalities described in this chapter have not been determined as we continue to assess the scope and determinants of the problem. Nevertheless, health-care providers need to be vigilant for signs of distress among patients with CLD and their families. Patient/parent interview should incorporate questions around cognitive and school functioning, as well as psychosocial functioning and overall HRQOL. Parental stress, adjustment,

Table 7.1 PedsQL™ 4.0 generic core scale scores by age at testing*

	Age at testing			
	<2 years ($n=259$)	2–4 years ($n=254$)	5–7 years ($n=244$)	≥8 years ($n=169$)
Scale score	**Median (interquartile range)**			
Total score ($p<0.0001$)	85.7 (73.8–94.4)	79.4 (63.0–90.2)	73.9 (59.8–84.2)	76.1 (59.8–88.0)
Physical health ($p<0.0001$)	93.8 (78.1–100.0)	87.5 (68.8–96.9)	83.3 (62.5–93.8)	81.3 (62.5–93.8)
Psychosocial health ($p<0.0001$)	82.7 (70.0–92.3)	76.7 (61.7–88.3)	69.2 (56.7–81.7)	73.3 (56.7–90.0)

*Unpublished data from the Functional Outcomes Group (FOG) research group, part of the Studies of Pediatric Liver Transplantation (SPLIT) collaborative

and family functioning should also be assessed (Table 7.2). Providers need to be particularly alert for these concerns in very young and very growth deficient patients, those who are the most ill, have a complicated course, or have an illness that causes more serious impairment (e.g., metabolic disorders). Providers need to recognize and prepare parents for the likelihood that any cognitive and academic challenges seen pre-transplant will persist following transplantation.

Table 7.2 Suggested interview/survey approach to screen for psychosocial, cognitive, and HRQOL concerns in pediatric patients with liver disease in the medical setting

Area of functioning	Parent ("Does your child have difficulty…")
Cognitive/motor	
Age 0–5	Speaking or understanding?
	Performing gross motor or fine motor activities such as walking, running, jumping, skipping, buttoning, tying laces, or drawing?
	[Use the Ages & Stages Questionnaires®]
Elementary school years	Concentrating, following directions, or remembering things?
	Understanding others or putting their thoughts into words?
	Understanding ideas that are not concrete or literal (things that are not obviously stated)?
	Performing gross motor or fine motor activities?
Middle/high school years (include patient in interview)	[Same as for elementary]
	Keeping their belongings organized?
	Using strategies to solve problems?
	Performing gross motor or fine motor activities?
Academic	
Preschool	Drawing or writing?
	Learning letters and letter sounds, numbers and counting, colors, and shapes?
	Learning phone number, address, parents' names?
	Writing their name?
Elementary school	With homework: taking longer, needing more help, working harder than same age peers?
	Remembering to bring home materials, complete assignments, and turn in completed work?
	Planning ahead on longer projects?
	Reading and understanding what they read?
	Putting ideas into writing?
	Understanding math concepts and problem-solving?
Middle/high school (include patient in interview)	[Same as for elementary]
	Learning new material: making it "stick"?
	Keeping school materials organized?
	Managing time efficiently?
	Studying effectively for tests?
	Checking work for careless errors?
	Working mostly independently?
Psychosocial	
Age 0–5	[Use the Ages & Stages Questionnaires®]
Elementary years	Making and keeping friends?
	Regulating mood (keeping mood "on an even keel" without getting overly excited, sad, or mad frequently)?
	Dealing with frustration?
	With fears and worries or self-esteem?
	Adjusting to changes?
	Understanding and accepting their medical condition/history?
	Controlling their behavior?

(continued)

Table 7.2 (continued)

Area of functioning	Parent ("Does your child have difficulty…")
Middle/high school	[Same as elementary]
	Adhering to medication/treatment regimen?
	Planning for future?
	Engaging in age-appropriate activities?
	Avoiding excessively risky behaviors?
	Self-advocating (e.g., asking questions, asking for help when needed, using available resources and supports)?
HRQOL	Use the PedsQL™

Patients with significant concerns should be referred for more comprehensive evaluation. Parents should also be screened for psychosocial concerns related to their child's illness and referred for treatment as needed

When cognitive/academic concerns are discovered, patients should be referred for neuropsychological evaluation or school-based testing so that they may receive special education services if warranted. Even if school performance is adequate in the early grades, parents should be vigilant for signs of increased difficulty keeping pace with academic demands and seek evaluation and/or services in a timely manner when such concerns arise. Since LT occurs most commonly prior to the start of formal education, teachers may not be aware of the child's history and the extent to which it may impact neuropsychological, academic, and psychosocial functioning.

Several websites provide information and resources regarding liver function and disorders in children. The Children's Liver Disease Foundation (www.childrensliverdisease.org), the American Liver Foundation (www.liverfoundation.org), and Children's Liver Association for Support Services (CLASS; www.classkids.org) provide informational handouts and resources. The Children's Liver Disease Foundation has appealing and kid-friendly animations explaining normal and abnormal liver functioning. The CLASS website provides numerous links to additional support organizations. UNOS (www.unos.org) provides statistics on LT and information for patients and families. The Childhood Liver Disease Research and Education Network (ChiLDREN) is a collaborative network of medical centers and patient support organizations designed to encourage and facilitate participation in research studies (http://childrennetwork.org).

Pediatric patients with liver disease clearly demonstrate deficits in IQ that typically persist even after LT. However, the longitudinal course of these deficits over the lifespan and in terms of time since LT is not well described. It is unclear which patients will improve after LT and which will remain stable. While IQ deficits are expected, more data is needed regarding the pattern of functioning across other cognitive domains. Attention/executive function is an area of particular interest given its importance to maintaining a job and independent living and its relationship to MHE. While lactulose and rifaximin are sometimes given in pediatric patients with suspected MHE, their effectiveness in children has not been examined using cognitive measures, as they have in adults [95]. These areas would benefit from further study.

Referral for a more thorough psychological evaluation may also be warranted if the child or parents express psychosocial concerns. Patients and families are negatively affected by the chronicity of liver disease and the fear and uncertainty therein. The complexity and burden of medical management of children with end-stage liver disease place enormous psychosocial and financial stress on patients and their families. Parents may be overwhelmed with the fear that their child may die suddenly or in the case of genetically acquired metabolic diseases that they are to blame. Disruption caused by frequent doctor's visits, the pain and prospects of unexpected complications associated with multiple medical procedures, and the difficulty in maintaining steady employment and a normal home

environment for the rest of their family members contribute to this struggle [1]. The demands of providing adequate health care to children with end-stage liver disease may quickly outstrip the family's resources. When this happens, social services must be involved to optimize provision of unmet psychosocial and financial needs to minimize further negative repercussions for the child. Transportation, housing, and financial arrangements can often be made to meet the family's immediate care-related needs. Early and intensive involvement of social and financial services is critical to maintaining good quality of life for these patients and families in order to ensure the best outcomes for this vulnerable patient population.

The transplant process is also a time of great stress for the entire family. Attention to the needs and concerns of the parents and other family members is essential. This may require consulting with social workers and psychologists. Further study is needed on how to best help families cope with these pressures and how they affect the medical outcome, particularly graft failure. HRQOL remains below that of the general population with school function of particular concern. The growing understanding of the relationship between HRQOL, medication adherence, and overall graft function underscores this as an area where successful interventions may lead to long-term medical and social benefits.

Once the scope and nature of the problems have been more comprehensively characterized, potential changes in policy (e.g., age at LT listing) and standard of care (e.g., use of post-LT medications, surgical interventions) can be proposed to promote optimal outcomes. Finally, when all modifiable medical variables contributing to cognitive and psychosocial outcomes have been addressed, research must pursue additional means for improving outcomes by assessing the efficacy of targeted interventions (e.g., psychostimulants for inattention). These goals can only be accomplished with more multicenter collaboration and efforts to carefully design prospective studies with large, representative samples. Use of different tests based on age in the same sample should be minimized or at least standardized as this introduces a confounder and makes interpretation more challenging. Psychosocial, cognitive, and HRQOL outcomes in children with liver disease and LT represent an underexplored frontline whose assessment will hopefully lead to a better understanding and more effective prevention and management of deficits in the coming years.

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