ORIGINAL ARTICLE

Relationship Between Sleep Problems and Health-Related Quality of Life Among Pediatric Liver Transplant Recipients

Emily M. Fredericks,[1] Dawn Dore-Stites,[1] Sheyla Y. Calderon,[1] Andrew Well,[1] Sally J. Eder,[1] John C. Magee,[2] and M. James Lopez[1]

Department of [1]Pediatrics and Communicable Diseases and [2]Surgery, University of Michigan Health System, Ann Arbor, MI

Among adult liver transplant recipients (LTRs), sleep disturbances and fatigue are common. Sleep problems following pediatric liver transplantation may contribute to daytime fatigue and lower health-related quality of life (HRQOL). The aim of this cross-sectional study was to determine the impact of sleep problems on the HRQOL of pediatric LTRs using validated measures. Participants included 47 LTRs. Mean age of the LTRs was 10.9 ± 4.6 years, and mean time since transplantation was 6.2 ± 3.9 years. The primary indication for transplantation was biliary atresia (51%). According to parent reports, pediatric transplant recipients had symptoms of sleep-disordered breathing, excessive daytime sleepiness, daytime behavior problems, and restless legs; 40.4% of parents and 43.8% of children reported significantly lower total HRQOL for the recipients. Age, time since transplantation, and health status were not significantly related to the quality of life. Hierarchical regression analyses revealed that the sleep-disordered breathing subscale of the Pediatric Sleep Questionnaire accounted for significant variance in parent-proxy reports on the Pediatric Quality of Life (PedsQL) summary scales measuring children's psychosocial health ($R^2 = 0.36$, $P < 0.001$), physical health ($R^2 = 0.19$, $P = 0.004$), and total HRQOL ($R^2 = 0.35$, $P < 0.001$). Also, the sleep-disordered breathing subscale accounted for significant variance in the child self-reported school functioning scale ($R^2 = 0.18$, $P = 0.03$). Clinically significant sleep problems were more common among children with low total HRQOL. In conclusion, sleep problems were common in this cohort of pediatric LTRs and predicted significant variance in HRQOL. Prospective larger scale studies are needed to assess factors that contribute to sleep difficulties and low HRQOL in this population. The detection and treatment of significant sleep problems may benefit the HRQOL of pediatric LTRs. ***Liver Transpl 18:707-715, 2012.*** © **2012 AASLD.**

Received November 23, 2011; accepted February 5, 2012.

Pediatric liver transplant recipients (LTRs) have lower health-related quality of life (HRQOL) than healthy children across domains of physical and psychosocial functioning[1-5] and particularly in the area of school functioning.[2,3] The risk factors predictive of lower HRQOL in pediatric LTRs are poorly understood.

Among adult LTRs, sleep disturbances and fatigue are common. A recent study examined the relationship between fatigue, sleep quality, and quality of life in adults before and after liver transplantation.[6] The study findings indicated that the majority of post-transplant patients (77%) had poor sleep quality, which was significantly related to a higher body mass

Abbreviations: HRQOL, health-related quality of life; LTR, liver transplant recipient; PedsQL, Pediatric Quality of Life; PLMS, periodic limb movements during sleep; PSQ, Pediatric Sleep Questionnaire; RLS, restless leg symptoms; SRBD, sleep-related breathing disorder.

This publication was made possible by a Career Development Award from the National Institute of Diabetes and Digestive and Kidney Diseases (grant 1K23DK090202-01 to Emily M. Fredericks).

Address reprint requests to Emily M. Fredericks, Ph.D., Department of Pediatrics and Communicable Diseases, University of Michigan Health System, 1500 East Medical Center Drive, 1924 Taubman Center, SPC 5318, Ann Arbor, MI 48109-5318. Telephone: 734-615-3866; FAX: 734-936-6897; E-mail: emfred@med.umich.edu

DOI 10.1002/lt.23415
View this article online at wileyonlinelibrary.com.
LIVER TRANSPLANTATION.DOI 10.1002/lt. *Published on behalf of the American Association for the Study of Liver Diseases*

index and anxiety. Moreover, high levels of fatigue and poor sleep quality were significantly associated with a lower quality of life before and after transplantation.[6] In a separate study, researchers similarly found that poor sleep quality and fatigue were common symptoms after liver transplantation in adult recipients.[7] A high rate of restless leg symptoms (RLS; 39%), a frequent cause of decreased sleep quality and quantity, has also been observed in adult LTRs.[8]

It is well documented that inadequate or disrupted sleep has detrimental effects on HRQOL, physical health, behavior, and learning in children with or without medical comorbidities.[9-14] Sleep problems after pediatric liver transplantation may contribute to daytime fatigue, lower HRQOL, cognitive difficulties, and behavioral disturbances. Thus, determining the prevalence of sleep problems in this population is important for promoting optimal long-term health. To date, no empirical investigations have been conducted to determine the prevalence of sleep problems in pediatric LTRs or their impact. The aim of this cross-sectional study was to determine the impact of sleep problems on pediatric LTRs' HRQOL.

PATIENTS AND METHODS

Study Population

Parents and pediatric LTRs were recruited from the Pediatric Liver Transplant Clinic at the University of Michigan to participate in an investigation of children's HRQOL, behavior, sleep quality, and health status after liver transplantation. All children between the ages of 2 and 17 years who had undergone liver transplantation more than 6 months ago were eligible for participation. Potential participants were identified through University of Michigan electronic medical records and were recruited during their Pediatric Liver Transplant Clinic visits.

Procedures

This study was a cross-sectional survey of sleep problems among pediatric LTRs. The institutional review board of the University of Michigan Medical School approved all aspects of the study. Parents or guardians completed standardized assessment measures of each patient's sleep problems and HRQOL during the child's Pediatric Liver Transplant Clinic appointment. To prevent a potential response bias, the order of survey administration was varied across participants. Children older than 8 years completed a self-report measure of HRQOL. Demographic and medical data were obtained from University of Michigan electronic medical records.

Measures

Pediatric Sleep Questionnaire (PSQ)[15]

The PSQ is a validated, parent-completed instrument that assesses multidimensional aspects of sleep in children who are 2 to 18 years old. The PSQ includes a 22-item sleep-related breathing disorder (SRBD) index, which assesses symptoms such as nighttime breathing difficulties (snoring), excessive daytime sleepiness (sleepiness), and inattentive-hyperactive behaviors (behavior).[15] The PSQ also contains a 6-item subscale measuring periodic limb movements during sleep (PLMS), including RLS and growing pains.[16]

The responses on the PSQ are *yes* (1), *no* (0), or *don't know* (missing). Scores on the PSQ represent the proportion of nonmissing items that are positive. A cutoff score of $\geq$0.33 (indicating that a patient is positive for 33% of the symptoms) is considered a positive screen.[15-17] The PSQ subscales have been validated against polysomnography and have demonstrated research and clinical utility.[15-18] The PSQ is classified as a well-established measure of pediatric sleep according to the criteria developed by the American Psychological Association Division 54 Evidence-Based Assessment Task Force.[19]

Pediatric Quality of Life (PedsQL) 4.0 Generic Core Scales[20]

The PedsQL is a validated, 23-item modular instrument designed to measure HRQOL in children and adolescents. The PedsQL assesses HRQOL across 4 domains: physical, emotional, social, and school functioning. The PedsQL also yields 3 summary scores: a total scale score, a physical health summary, and a psychosocial health summary. It is a 5-level Likert item survey (0-4) with reversed scored answers that are linearly transformed to a 0 to 100 scale, with higher scores reflecting higher HRQOL. The published validation study identified a value 1 standard deviation below the population mean for the PedsQL total score (69.7 for children's self-reports and 65.4 for parent-proxy reports) as a threshold score for an at-risk status for impaired HRQOL in comparison with the population sample.[21]

Health Status Variables

The health status variables obtained for each participant were the number of acute cellular rejection episodes in the year before participation, the time since transplantation, the results of liver function tests (total bilirubin, aspartate aminotransferase, and alanine aminotransferase), and the number of immunosuppressants at the time of participation.

Statistical Methods

Descriptive statistics (ie, means, standard deviations, and percentages) were determined for demographic variables, health status variables, PSQ subscales, and PedsQL subscales. The prevalence of sleep problems was calculated with the proportion of positive symptom items on the PSQ subscales.[15,22] Paired sample *t* tests were used to assess statistical differences

between the parent-reported and child-reported HRQOL. Hierarchical multiple regression analyses examining the contribution of sleep problems (as measured by the PSQ) to children's HRQOL were conducted in order to test the primary hypothesis.

Finally, differences in scores on the PSQ between children with high HRQOL and children with low HRQOL (as measured by the PedsQL total score) were examined with independent sample *t* tests. All analyses were conducted with SPSS 18.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Participant Characteristics

The participants included 47 LTRs. Clinical and demographic information is presented in Table 1. The mean age of the patients at the time of study participation was 10.9 ± 4.6 years (range = 2-17.6 years, median = 11.2 ± 4.6 years), and the mean time since transplantation was 6.2 ± 3.9 years (range = 7 months to 15.4 years, median = 5.6 ± 3.9 years). The majority of the patients were white (55%) and female (55%). The primary indication for transplantation was biliary atresia (51%), and the primary immunosuppressant medication was tacrolimus (98%).

Prevalence of Sleep-Related Symptoms in Pediatric LTRs

According to parent reports, pediatric LTRs in this study had symptoms of sleep-disordered breathing, excessive daytime sleepiness, daytime behavior difficulties, and restless legs (Table 2).

The mean SRBD score for the sample of LTRs was 0.23 ± 0.16, which indicated that 23% of the subscale items were positive. A score suggestive of SRBD was found in 11 children (23.4%). The mean PLMS/RLS index score was 0.23 ± 0.21, with 14 participants (29.8%) exceeding the clinical cutoff score.

With respect to the PSQ subscales that compose the SRBD index, the mean snoring subscale score was 0.17 ± 0.27, and habitual snoring, which was defined as snoring more than half the time, was reported for 8 children (17.0%). The mean excessive daytime sleepiness subscale score for LTRs was 0.28 ± 0.30, with 19 participants (40.4%) exceeding the clinical cutoff score of 0.33. Lastly, the mean behavior index score for the pediatric liver transplant cohort was 0.30 ± 0.33. Significant symptoms of inattention and hyperactivity were reported for 20/44 pediatric LTRs (45.5%). Snoring was significantly related to younger age ($r = -0.34$, $P = 0.02$). There were no other significant associations with age, sex, or time since transplantation. There were no significant differences across the sleepiness, PLMS/RLS, or behavior domains with respect to age, sex, or time since transplantation.

TABLE 1. Characteristics of Pediatric LTRs (n = 47)

Age (years)*	10.9 ± 4.6
Time since transplantation (years)*	6.2 ± 3.9
Sex [n (%)]	
Female	26 (55)
Male	21 (45)
Race [n (%)]	
White	26 (55)
African American	14 (30)
Other	7 (15)
Diagnosis [n (%)]	
Biliary atresia	24 (51)
Acute liver failure	6 (13)
Hepatoblastoma	3 (6)
Alagille syndrome	2 (4)
Choledochal cyst	2 (4)
Argininosuccinic aciduria	2 (4)
Alpha-1-antitrypsin deficiency	1 (2)
Autoimmune hepatitis	1 (2)
Budd-Chiari syndrome	1 (2)
Byler syndrome	1 (2)
Hemangioendothelioma	1 (2)
Tyrosinemia	1 (2)
Progressive familial intrahepatic cholestasis	1 (2)
Nonalcoholic steatohepatitis	1 (2)
Immunosuppressant medications [n (%)]†	
Tacrolimus	45 (95.7)
Mycophenolate mofetil (CellCept)	13 (27.7%)
Prednisone	10 (21.3%)
Cyclosporine	2 (4.3%)
Rejection episodes [n (%)]	
None	39 (83)
1	7 (15)
2	1 (2)

*The data are presented as means and standard deviations.

†Twenty-eight (57.6%) of the 47 participants were prescribed only tacrolimus; 2 (4.3%) were prescribed only cyclosporine; 7 (14.9%) were prescribed tacrolimus and mycophenolate mofetil; 4 (8.5%) were prescribed tacrolimus and prednisone; and 6 (12.8%) were prescribed tacrolimus, mycophenolate mofetil, and prednisone.

TABLE 2. Pediatric LTRs With Significant Sleep Problems as Measured by the PSQ

	Yes (Score ≥0.33)	No (Score < 0.33)
SRBD index (%)	23.4	76.6
Snoring subscale	17.0	83.0
Sleepiness subscale	40.4	59.6
Behavior subscale*	45.5	54.5
PLMS/RLS index (%)	29.8	70.2

*$N = 44$ for the Behavior subscale.

HRQOL

No significant differences were found between parent-proxy reports and children's self-reported quality of

TABLE 3. Regression Analyses of Parent-Proxy Reports of Children's HRQOL and SRBD

Model	PedsQL 4.0	Step	Variable	β	*t* for Within-Step Predictors	R^2	R^2 Change for Step	*F* Change	Significance
1	Total HRQOL	1	Age	−0.10	−0.06	0.02	0.02	0.33	0.72
			Time since transplantation	−0.03	−0.15				
		2	SRBD	−0.60*	−4.7	0.35	0.33	21.9*	<0.001
2	Psychosocial health	1	Age	−0.06	−0.35	0.02	0.02	0.034	0.71
			Time since transplantation	−0.07	−0.41				
		2	SRBD	−0.61*	−4.81	0.36	0.35	23.16*	<0.001
3	Physical functioning	1	Age	−0.17	−0.93	0.02	0.02	0.44	0.65
			Time since transplantation	0.09	0.47				
		2	SRBD	−0.44*	−3.04	0.19	0.17	9.24*	0.004
4	Emotional functioning	1	Age	−0.01	−0.03	0.02	0.02	0.48	0.62
			Time since transplantation	−0.14	−0.79				
		2	SRBD	−0.5*	−3.62	0.25	0.23	13.10*	0.001
5	Social functioning	1	Age	−0.01	−0.05	0.003	0.003	0.07	0.93
			Time since transplantation	−0.05	−0.28				
		2	SRBD	−0.42*	−2.86	0.16	0.16	8.17*	0.007
6	School functioning	1	Age	−0.08	−0.44	0.005	0.005	0.10	0.91
			Time since transplantation	0.03	0.17				
		2	SRBD	−0.63*	−4.89	0.38	0.37	23.88*	<0.001

*$P < 0.001$.

life on the PedsQL. With the published cutoff scores of 65.4 for parent-proxy reports and 69.7 for children's self-reports, 40.4% of parents and 43.8% of children reported low total HRQOL. Age, time since transplantation, and health status variables were not significantly related to the quality of life.

Relationship Between Sleep Problems and HRQOL

Parent-Proxy Reports of Children's HRQOL

Hierarchical regression analyses were conducted to examine the contribution of SRBD to parent-proxy reports of children's HRQOL. Age and time since transplantation were entered as block 1, and the SRBD scale was entered as block 2. The regression analyses revealed that the SRBD subscale of the PSQ accounted for significant variance in parent-proxy reports on the PedsQL summary scales measuring children's psychosocial health ($R^2 = 0.36$, $P < 0.001$), physical health ($R^2 = 0.19$, $P = 0.004$), and total HRQOL ($R^2 = 0.35$, $P < 0.001$). In addition, SRBD accounted for significant variance across all subscales of the parent-proxy PedsQL measure (Table 3).

To determine which domain of the PSQ had the greatest impact on the quality of life, the sleepiness, snoring, PLMS/RLS, and behavior subscale scores were entered into hierarchical regression analyses. Age and time since transplantation were entered as block 1 in the overall HRQOL model. Sleepiness, snoring, PLMS/RLS, and behavior scores were entered as block 2. There were no significant associations between the health status variables and the quality of life or sleep at the bivariate level, so health status variables were not entered into the regression analyses (Table 4).

Children's Self-Reports of HRQOL

Hierarchical regression analyses were conducted to examine the contribution of SRBD to children's self-reported HRQOL. Age and time since transplantation were entered as block 1, and the SRBD scale was entered as block 2. Regression models for the psychosocial health, physical health, and total HRQOL summary scales were not significant. Across the subscales of the PedsQL, the SRBD scale accounted for significant variance on the self-reported school functioning scale ($R^2 = 0.18$, $P = 0.03$). There were no other significant associations between children's reported HRQOL and the SRBD scale, age, or time since transplantation.

To explore which domain of the PSQ had the greatest impact on the school functioning domain of the PedsQL, subscale scores were entered into a hierarchical linear regression as described previously. This regression model did not account for significant variance in children's HRQOL ($R^2 = 0.28$, $P = 0.11$).

TABLE 4. Hierarchical Regression Analyses of Sleep Problems and Parent-Proxy Reports of Children's HRQOL

Model	PedsQL Domain	Step	Variable	β	*t* for Within-Step Predictors	R^2 Change for Step	*F* Change	Significance
1	Total HRQOL	1	Age	−0.54	−0.29	0.009	0.009	0.84
			Time since transplantation	−0.52	−0.28			
		2	Snoring	−0.12	−0.847	0.366	5.410*	0.002
			Excessive daytime sleepiness	−0.20	−1.22			
			PLMS/RLS	−0.30	−1.87†			
			Behavior	−0.27	−1.78†			
2	Psychosocial functioning	1	Age	−0.01	−0.03	0.01	0.17	0.84
			Time since transplantation	−0.09	−0.48			
		2	Snoring	−0.14	−0.95	0.36	5.20*	<0.001
			Excessive daytime sleepiness	−0.18	−1.09			
			PLMS/RLS	−0.30	−1.85†			
			Behavior	−0.27	−1.80†			
3	Physical functioning	1	Age	−0.16	−0.86	0.02	0.40	0.67
			Time since transplantation	0.04	0.24			
		2	Snoring	−0.07	−0.43	0.22	2.69‡	0.05
			Excessive daytime sleepiness	−0.20	−1.11			
			PLMS/RLS	−0.22	−1.25			
			Behavior	−0.18	−1.11			
4	Emotional functioning	1	Age	0.03	0.16	0.02	0.32	0.73
			Time since transplantation	−0.14	−0.75			
		2	Snoring	−0.23	−1.53	0.33	4.61*	<0.001
			Excessive daytime sleepiness	−0.09	−0.53			
			PLMS/RLS	−0.36	−2.21‡			
			Behavior	−0.14	−0.93			
5	Social functioning	1	Age	−0.03	−0.14	0.01	0.17	0.84
			Time since transplantation	−0.08	−0.41			
		2	Snoring	−0.05	−0.28	0.22	2.63‡	0.05
			Excessive daytime sleepiness	−0.08	−0.45			
			PLMS/RLS	−0.32	−1.81†			
			Behavior	−0.22	−1.30			
6	School functioning	1	Age	0.10	0.56	0.01	0.25	0.78
			Time since transplantation	0.02	0.13			
		2	Snoring	−0.06	−0.36	0.30	3.73*	0.01
			Excessive daytime sleepiness	−0.25	−1.41			
			PLMS/RLS	−0.09	−0.53			
			Behavior	−0.37	−2.17‡			

*$P < 0.01$.
†$P < 0.1$.
‡$P < 0.05$.

Between-Group Comparisons

To determine whether sleep problems were differentially present between children with a high quality of life and children with a low quality of life, we conducted between-group analyses with the published cutoff scores of 65.4 for parent-reported total HRQOL and 69.7 for self-reported total HRQOL. Clinically significant sleep problems on the PSQ (cutoff score ≥ 0.33) were more common among children with low total HRQOL (Table 5). There were no significant

group differences according to children's self-reports. According to parental reports, there were significant differences between the high-HRQOL group and the low-HRQOL group across all domains of the PSQ except snoring (Fig. 1).

Sleep Problems and Health Status

The snoring subscale of the PSQ was negatively correlated with a child's age ($r = -0.33$, $P = 0.02$) and was positively correlated with aspartate aminotransferase ($r = 0.37$, $P = 0.01$) and total bilirubin ($r = 0.43$, $P = 0.003$). There were no significant associations between the remaining subscales of the PSQ and a child's age, time since transplantation, weight, height, body mass index, liver function tests, or immunosuppressant medications.

To determine whether elevations on the SRBD scale, which includes questions related to snoring, were related to tonsillar hypertrophy, we conducted a chart review for the 11 patients with SRBD scores in the clinical range (>0.33). Four of these patients had undergone tonsillectomy with adenoidectomy (n = 3) or without adenoidectomy (n = 1) because of tonsillar hypertrophy, elevated Epstein-Barr virus levels, and (in 1 patient) a history of posttransplant lymphoproliferative disease; the remaining 7 patients did not have evidence of elevated Epstein-Barr virus levels or tonsillar hypertrophy. There was no significant difference in SRBD scores between patients who had significant Epstein-Barr virus/tonsillar hypertrophy and those who did not ($P = 0.07$).

TABLE 5. Children With Significant Sleep Problems by the HRQOL Level as Measured by Parent-Proxy Reports on the PedsQL

PSQ Domain	High Total HRQOL (>65.43)	Low Total HRQOL (≤65.43)
SRBD index (%)	10.0	42.0
Snoring subscale	14.0	21.0
Sleepiness subscale	21.0	68.0
Behavior subscale	32.0	57.9
RLS/PLMS index (%)	17.9	47.0

DISCUSSION

This study examined the prevalence of sleep problems in pediatric LTRs and the impact of sleep problems on HRQOL. According to parental reports, sleep-related disturbances and daytime behavior difficulties were prevalent in our cohort of pediatric LTRs. The results of this study are consistent with existing literature indicating that pediatric LTRs have low HRQOL in comparison with healthy peers.[3] Approximately 40% of the participants had a substandard quality of life according to parental reports and/or self-reports. Likewise, daytime behavior problems consistent with symptoms of inattention/hyperactivity were reported at a high frequency. It was unclear whether these daytime symptoms were secondary to poor sleep or were related to cognitive dysfunction.[23,24]

Sleep disturbances were common in our sample. Nearly 25% of the parents endorsed clinically significant symptoms of SRBD in their children. This was significantly higher than the rate of 11% observed in a general pediatric clinic sample.[18] When we examined

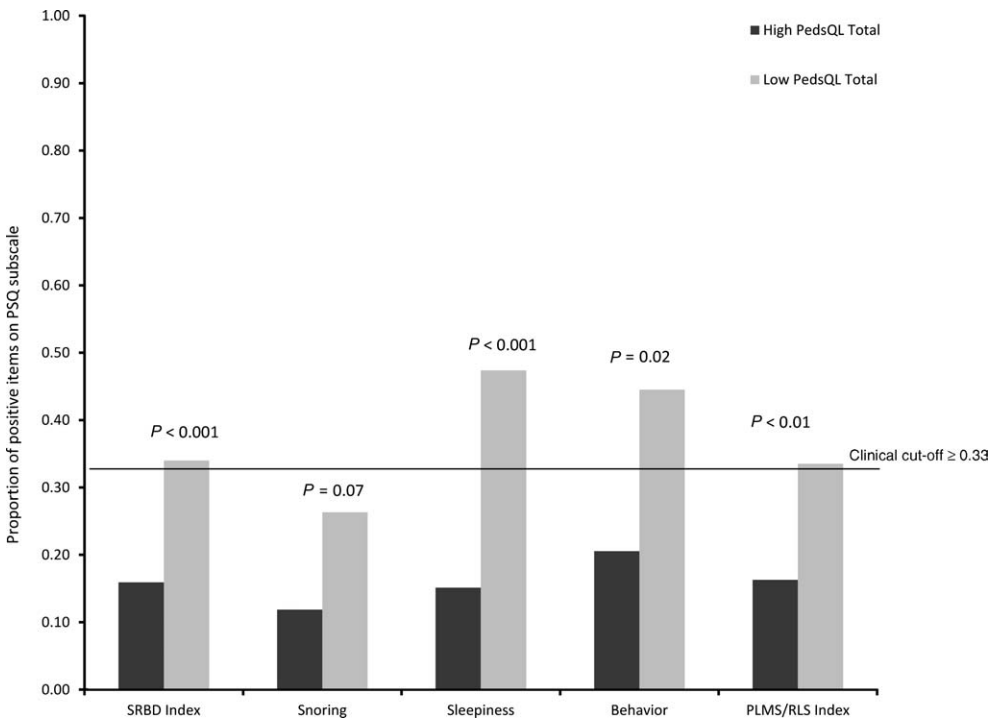

Figure 1. Comparison of sleep problems in children with high HRQOL and children with low HRQOL according to parent-proxy reports on the PedsQL.

the components of the SRBD scale, it appeared that excessive daytime sleepiness was a significant contributor to the elevated scores on this index. Indeed, the rate for snoring, which is a primary symptom of SRBD, was comparable to the rate previously reported for children (17%).[18] In contrast, excessive daytime sleepiness was reported in nearly half of our sample of pediatric LTRs; this is more than double the rate observed among children presenting for well-child visits.[18] This suggests that daytime sleepiness is a significant concern among pediatric LTRs. In addition, nearly a third of the pediatric LTRs in this study exceeded clinical cutoff scores on the PLMS/RLS index. This rate is significantly higher than the rates of 2% to 17% observed in population-based[23] and community-based pediatric samples.[25] Preliminary research among adult LTRs suggests that poor sleep quality, fatigue, and RLS are common after transplantation.[6-8] The associations between RLS, fatigue, and HRQOL in a pediatric transplant population remain an area for further study.

In studies of adult LTRs, symptoms of sleep difficulties have been related to a higher body mass index and mood disorders.[6,7] In this study, sleep difficulties were not related to the body mass index, time since transplantation, or other measured health status variables. It is surprising that the child's health status, as measured in this study, was not related to measures of perceived HRQOL or sleep disruption. This could be related to the possibility that perceived sleep problems and poor HRQOL in this population are associated not with physical health problems but rather behavioral/emotional health problems. The causes of daytime fatigue and PLMS/RLS in our pediatric liver transplant population are unknown. There are various factors that may contribute to poor sleep quality in children, including poor sleep hygiene, mood disturbances, obesity, and underlying primary sleep disorders (eg, obstructive sleep apnea or PLMS/RLS).[15,26-28] With respect to PLMS/RLS, which can have a substantial impact on sleep quality and quantity, the etiology in pediatric populations is not definitive. Research suggests that serum ferritin levels less than 50 ng/mL may contribute to the severity of RLS symptoms.[29] Moreover, because of the association between RLS/PLMS and attention deficit/hyperactivity disorder,[25] it has been hypothesized that a lower iron status and dopaminergic mechanisms are common factors in the pathophysiology of these conditions.[29] Because of the high rates of RLS and daytime behavior difficulties reported in this study sample, the further investigation of potential risk factors such as suboptimal ferritin levels is warranted.

Medications can also contribute to sleep disturbances. Indeed, steroids have been shown to be associated with sleep disturbances,[30,31] and tacrolimus, a calcineurin inhibitor, has been associated with neuropsychological and behavioral side effects and insomnia in pediatric renal transplant recipients.[32] In this study, scores on the PSQ were unrelated to the types of immunosuppressant medications. However, very few participants were receiving a steroid treatment (n = 10). Further large-scale studies are required to elucidate potential predictors of sleep disturbances, including PLMS/RLS and daytime fatigue, in a pediatric transplant population.

When we examined the impact of sleep problems on HRQOL, we found that a disproportionate number of children with significant sleep problems were among those with low total HRQOL on the PedsQL. The SRBD scale, which measures nighttime breathing difficulties, excessive daytime sleepiness, and inattentive-hyperactive behaviors, accounted for significant variance in children's quality of life. Further analyses revealed that the subscales measuring excessive daytime sleepiness and symptoms of periodic limb movement and restless legs had the greatest impact on quality of life. Child-reported school functioning was most affected by the daytime behavioral domain of the SRBD.

The results of our preliminary study suggest that pediatric LTRs may be at increased risk for sleep problems, daytime sleepiness, and associated daytime behavioral difficulties, which have the potential to negatively affect HRQOL. Among healthy children, sleep problems are associated with increased daytime behavior problems, emotional difficulties, and academic and cognitive deficits.[33-35] There is increasing research supporting the idea that pediatric LTRs are at risk for poor school functioning[36,37] and low HRQOL.[3] However, modifiable factors contributing to deficits in cognitive functioning and HRQOL remain relatively unknown. It is possible that lower HRQOL could be ameliorated by the identification and treatment of sleep problems and daytime sleepiness.

Untreated sleep disorders may lead to poor health outcomes, including potentially deleterious effects on the cardiovascular and immune systems.[28,38,39] In addition, the correlation of sleep problems and lower HRQOL raises the possibility that interventions aimed at improving sleep[12,40-42] could potentially have a positive impact on academic and behavioral functioning in pediatric LTRs. Thus, the screening and appropriate treatment of sleep disorders among pediatric LTRs may contribute to better long-term health outcomes.

Our study was limited because it was a small, cross-sectional, single-center study. The ability to detect group differences based on children's self-reports was limited by insufficient power. Moreover, sleep problems were measured with a subjective questionnaire completed by parents and not with objective measures of sleep disruption such as overnight polysomnography. Moreover, the association between sleep and HRQOL is unlikely to be unidirectional. Individuals with poor HRQOL, particularly in the areas of emotional functioning, may have increased risk for sleep difficulties, including insomnia and daytime fatigue. Likewise, this study did not investigate the level of family distress, which may also affect a

child's HRQOL and sleep patterns. Because the measures used in this study have not been validated in children less than 2 years of age, we did not assess sleep disruption and perceived quality of life for pediatric LTRs less than 2 years of age. It is premature to generalize the findings of this study to the very young pediatric LTR population. Nonetheless, these data suggest that there is a need for increased awareness of sleep disturbances among clinicians who care for pediatric LTRs. Further prospective, multicenter studies are needed to determine underlying factors contributing to the association between sleep disturbances and poor HRQOL in pediatric LTRs.

Despite the limitations, the results of this pilot study have potential clinical implications. On the basis of the early results of this study, our clinic has begun to routinely screen patients for the presence of sleep problems with the BEARS (Breathing, Excessive sleepiness, Awakenings, Regularity, Snoring) screening method, which briefly assesses patients for breathing, excessive sleepiness, arousal, regularity of sleep, and snoring.[43] Patients who have positive screens are referred to our pediatric sleep clinic for further evaluation and treatment as needed. We continue to prospectively study sleep both before and after transplantation to identify prevalence rates and potential risk factors. Future directions include the use of objective sleep measures such as polysomnography and actigraphy.

In summary, sleep problems were common in this cohort of pediatric LTRs and predicted significant variance in parent-proxy reports of HRQOL. At this point, it remains unclear whether this association is mediated by symptoms of underlying sleep disorders, excessive daytime sleepiness, or associated daytime behavior problems. However, the significant relationships between sleep difficulties and HRQOL provide guidance for future assessments and interventions because sleep disorders are readily modifiable. Prospective larger scale studies are needed to assess factors that may lead to sleep difficulties and low HRQOL in this population. The appropriate detection of significant sleep problems may lead to interventions that could benefit the quality of life of pediatric LTRs.

ACKNOWLEDGMENTS

The authors thank the families that volunteered to participate in this project. They also acknowledge the contributions of Rebecca Gleit, Radhika Raghunathan, and Veronica Juan and thank Dr. Louise O'Brien for her thoughtful review of a previous version of this article.

REFERENCES

1. Bucuvalas JC, Britto M, Krug S, Ryckman FC, Atherton H, Alonso MP, et al. Health-related quality of life in pediatric liver transplant recipients: a single-center study. Liver Transpl 2003;9:62-71.
2. Fredericks EM, Magee JC, Opipari-Arrigan L, Shieck V, Well A, Lopez MJ. Adherence and health-related quality of life in adolescent liver transplant recipients. Pediatr Transplant 2008;12:289-299.
3. Alonso EM, Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, Varni JW; for Studies of Pediatric Liver Transplantation (SPLIT) Functional Outcomes Group (FOG). Cross-sectional analysis of health-related quality of life in pediatric liver transplant recipients. J Pediatr 2010;156:270-276.
4. Alonso EM, Neighbors K, Mattson C, Sweet E, Ruch-Ross H, Berry C, Sinacore J. Functional outcomes of pediatric liver transplantation. J Pediatr Gastroenterol Nutr 2003; 37:155-160.
5. Weissberg-Benchell J, Zielinski TE, Rodgers S, Greenley RN, Askenazi D, Goldstein SL, et al. Pediatric health-related quality of life: feasibility, reliability and validity of the PedsQL transplant module. Am J Transplant 2010; 10:1677-1685.
6. Walters AS, Pichietti D, Chervin RD, Konofal E. Childhood and adult factors associated with restless legs syndrome (RLS) diagnosis. Sleep Med 2009;10:267-268.
7. van Ginneken BT, van den Berg-Emons RJ, van der Windt A, Tilanus HW, Metselaar HJ, Stam HJ, Kazemier G. Persistent fatigue in liver transplant recipients: a two-year follow-up study. Clin Transplant 2010;24: E10-E16.
8. Franco RA, Rizvi SM, Franco J, Graf L, Rizvi F. Excess prevalence of RLS in liver transplant recipients—a tertiary care center experience [abstract 0890]. Sleep 2010; 33(suppl):A298.
9. Hart CN, Palermo TM, Rosen CL. Health-related quality of life among children presenting to a pediatric sleep disorders clinic. Behav Sleep Med 2005;3:4-17.
10. Shin C, Kim J, Lee S, Ahn Y, Joo S. Sleep habits, excessive daytime sleepiness and school performance in high school students. Psychiatry Clin Neurosci 2003;57:451-453.
11. Sadeh A, Gruber R, Raviv A. Sleep, neurobehavioral functioning, and behavior problems in school-age children. Child Dev 2002;73:405-417.
12. Lima Júnior JM, Silva VC, Freitas MR. Long term results in the life quality of children with obstructive sleep disorders submitted to adenoidectomy/adenotonsillectomy. Braz J Otorhinolaryngol 2008;74:718-724.
13. O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Smith NH, McNally N, et al. Neurobehavioral correlates of sleep-disordered breathing in children. J Sleep Res 2004;13:165-172.
14. Bourke R, Anderson V, Yang JS, Jackman AR, Killedar A, Nixon GM, et al. Cognitive and academic functions are impaired in children with all severities of sleep-disordered breathing. Sleep Med 2011;12:489-496.
15. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric Sleep Questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 2000;1:21-32.
16. Chervin RD, Hedger KM. Clinical prediction of periodic leg movements during sleep in children. Sleep Med 2001;2:501-510.
17. Chervin RD, Weatherly RA, Ruzicka DL, Burns JW, Giordani BJ, Dillon JE, et al. Subjective sleepiness and polysomnographic correlates in children scheduled for adenotonsillectomy vs other surgical care. Sleep 2006; 29:495-503.
18. Archbold KH, Pituch KJ, Panahi P, Chervin RD. Symptoms of sleep disturbances among children at two general pediatric clinics. J Pediatr 2002;140:97-102.
19. Lewandowski AS, Toliver-Sokol M, Palermo TM. Evidence-based review of subjective pediatric sleep measures. J Pediatric Psychol 2011;36:780-793.
20. 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. Med Care 2001;39:800-812.

21. 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.
22. Chervin RD, Archbold KH, Panahi P, Pituch KJ. Sleep problems seldom addressed at two general pediatric clinics. Pediatrics 2001;107:1375-1380.
23. Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L. Restless legs syndrome: prevalence and impact in children and adolescents—the Peds REST study. Pediatrics 2007;120:253-266.
24. Picchietti DL, Stevens HE. Early manifestations of restless legs syndrome in childhood and adolescence. Sleep Med 2008;9:770-781.
25. Chervin RD, Archbold KH, Dillon JE, Pituch KJ, Panahi P, Dahl RE, Guilleminault C. Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. Sleep 2002;25: 213-218.
26. Chervin RD, Archbold KH, Dillon JE, Panahi P, Pituch KJ, Dahl RE, Guilleminault C. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics 2002;109:449-456.
27. Goodwin JL, Vasquez MM, Silva GE, Quan SF. Incidence and remission of sleep-disordered breathing and related symptoms in 6- to 17-year old children—the Tucson Children's Assessment of Sleep Apnea study. J Pediatr 2010;157:57-61.
28. Owens J. Classification and epidemiology of childhood sleep disorders. Prim Care 2008;35:533-546.
29. Picchietti MA, Picchietti DL. Restless legs syndrome and periodic limb movement disorder in children and adolescents. Semin Pediatr Neurol 2008;15:91-99.
30. Turner R, Elson E. Sleep disorders. Steroids cause sleep disturbance. BMJ 1993;306:1477-1478.
31. Chrousos GA, Kattah JC, Beck RW, Cleary PA. Side effects of glucocorticoid treatment. Experience of the Optic Neuritis Treatment Trial. JAMA 1993;269: 2110-2112.
32. Kemper MJ, Spartà G, Laube GF, Miozzari M, Neuhaus TJ. Neuropsychologic side-effects of tacrolimus in pediatric renal transplantation. Clin Transplant 2003;17: 130-134.
33. Curcio G, Ferrara M, De Gennaro L. Sleep loss, learning capacity and academic performance. Sleep Med Rev 2006;10:323-337.
34. Chorney DB, Detweiler MF, Morris TL, Kuhn BR. The interplay of sleep disturbance, anxiety, and depression in children. J Pediatr Psychol 2008;33:339-348.
35. Chung KF, Cheung MM. Sleep-wake patterns and sleep disturbance among Hong Kong Chinese adolescents. Sleep 2008;31:185-194.
36. Krull K, Fuchs C, Yurk H, Boone P, Alonso E. Neurocognitive outcome in pediatric liver transplant recipients. Pediatr Transplant 2003;7:111-118.
37. Gilmour S, Adkins R, Liddell GA, Jhangri G, Robertson CM. Assessment of psychoeducational outcomes after pediatric liver transplant. Am J Transplant 2009;9: 294-300.
38. Smaldone A, Honig JC, Byrne MW. Sleepless in America: inadequate sleep and relationships to health and well-being of our nation's children. Pediatrics 2007;119(suppl 1):S29-S37.
39. Horne RS, Yang JS, Walter LM, Richardson HL, O'Driscoll DM, Foster AM, et al. Elevated blood pressure during sleep and wake in children with sleep-disordered breathing. Pediatrics 2011;128:e85-e92.
40. Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ. Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. J Clin Sleep Med 2009;5: 355-362.
41. Owens JA, Moturi S. Pharmacologic treatment of pediatric insomnia. Child Adolesc Psychiatr Clin N Am 2009; 18:1001-1016.
42. Mitchell RB, Boss EF. Pediatric obstructive sleep apnea in obese and normal-weight children: impact of adenotonsillectomy on quality-of-life and behavior. Dev Neuropsychol 2009;34:650-661.
43. Owens JA, Dalzell V. Use of the 'BEARS' sleep screening tool in a pediatric residents' continuity clinic: a pilot study. Sleep Med 2005;6:63-69.