American Journal of Transplantation 2007; 7: 1974–1983
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2007.01878.x

Psychological Functioning, Nonadherence and Health Outcomes After Pediatric Liver Transplantation

E. M. Fredericks[a,*], M. J. Lopez[a], J. C. Magee[b], V. Shieck[c] and L. Opipari-Arrigan[a]

[a] *Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI*
[b] *Department of Surgery, University of Michigan Medical School, Ann Arbor, MI*
[c] *Transplant Center, University of Michigan Medical School, Ann Arbor, MI*
* *Corresponding author: Emily M. Fredericks, emfred@med.umich.edu*

The present study empirically assessed the relationships between adherence behaviors and HRQOL, parent and child psychological functioning and family functioning, and investigated the relationship between adherence behaviors and health outcomes in children who were within 5 years of their liver transplantation. Participants included 38 children (mean = 8.5 years, range 28 months to 16 years) and their parent/guardian(s). HRQOL and psychological functioning were examined using well-validated assessment measures. Measures of adherence included the rate of clinic attendance and standard deviations (SDs) of consecutive tacrolimus blood levels, which were collected and evaluated retrospectively. Measures of child health status included the frequency of hospital admissions, liver biopsies, episodes of rejection and graft function for the year prior to study participation. Results indicated that nonadherence was related to lower physical HRQOL, more limitations in social and school activities related to emotional and behavioral problems, parental emotional distress and decreased family cohesion. Nonadherence was also related to frequency and duration of hospitalizations, liver biopsies and rejection episodes. These results suggest that empirically based assessment of HRQOL, parenting stress and family functioning may help identify patients at risk for nonadherence, and may allow for the need-based delivery of appropriate clinical interventions.

Key words: Adherence, children, liver transplantation, quality of life

Received 15 December 2006, revised 6 April 2007 and accepted for publication 26 April 2007

Introduction

Post-transplant medical regimen adherence is essential for long-term graft survival, and poor adherence with post-transplant immunosuppressant medications is associated with increased medical complications, graft rejection, post-transplant mortality and increased health care utilization rates (1–4). Among pediatric liver transplant (LT) populations, nonadherence with post-operative medical regimens is estimated to be as high as 50% and contributes to more graft loss than uncontrolled rejection in adherent patients (3,4). These nonadherence rates are striking given that unlike other post-transplant complications, adherence behavior has the potential to be directly modifiable.

Given the severity of potential consequences of nonadherence, adherence behavior should be the focus of intervention. Before adherence-enhancing interventions can be developed, it is necessary to identify factors related to nonadherence among pediatric transplant recipients. Research with other pediatric chronic illness populations have identified poor health-related quality of life (HRQOL), parental psychological distress and disrupted family functioning as key constructs related to nonadherence (5) (see Table 1). Few empirically sound studies have examined these relationships in pediatric solid organ transplantation.

A recent review of 11 published studies that examined HRQOL in pediatric LT recipients suggested that LT recipients had poorer quality of life in some areas of physical, psychological, social and family functioning when compared to healthy peers, but equal to or better HRQOL than children with other chronic illnesses (6–9). Yet, the extent to which diminished HRQOL following transplant impacts adherence remains unclear.

The few studies that have examined the psychosocial functioning of parents of LT patients have demonstrated that parents of LT recipients report more emotional disturbances, including symptoms of post-traumatic stress disorder (PTSD), anxiety and depression (9–12) and more disrupted family activities than parents in the general population (8). To date, there is only one published study examining the relationship between parent functioning and post-transplant regimen adherence among LT recipients (11). This study found that parent symptoms of PTSD were significantly related to nonadherence as measured by clinician panel and standard deviations (SDs) of tacrolimus blood levels.

Regimen nonadherence has been linked to family variables such as poor family cohesion and greater stress levels

Table 1: Definitions of child HRQOL, parent and family functioning

Construct	Definition	Assessment tools
Health-related Quality of Life (HRQOL)	HRQOL is a multi-dimensional concept that reflects the impact of disease and treatment on an individual's subjective evaluation of his or her functioning and emotional well-being (28) Measurement of HRQOL includes an assessment of physical health, psychological health, social functioning, role (school) functioning and general health perceptions	Pediatric Quality of Life Inventory-Generic Core Scales (PedsQL4.0) (14) Child Health Questionnaire-Parent Form 50 (CHQ-PF50©) (15)
Child Psychological Functioning	Emotional and behavioral functioning including the degree of externalizing problems such as aggression, oppositional defiance, delinquency, inattention, hyperactivity, and impulsivity and internalizing behavior problems such as anxiety, depression, social withdrawal	Child Behavior Checklist (CBCL) Parent Report Form (16,17)
Parent Psychological Functioning	Anxiety, depression, and stress related to parenting a child with a chronic illness	Brief Symptom Inventory (18) Beck Depression Inventory (19) Pediatric Inventory for Parents (PIP) (20) CHQ-PF50©(15)
Family Functioning	The frequency of disruption of usual family activities, effectiveness of family communication and problem-solving, and degree of family cohesiveness, or how well the family gets along with one another	Family Assessment Device (21) Family Environment Scale (FES) (22) CHQ-PF50©(15)

(13). Yet, there is a lack of research investigating overall family functioning among pediatric transplant populations. Moreover, there are no published studies examining the effect of family functioning on adherence in a pediatric LT population.

The objectives of the current study were to assess the relationships between adherence and HRQOL, parent and child psychological functioning, and family functioning using empirically validated assessment measures, and to investigate the relationship between adherence and health outcomes in children who were within 5 years of their liver transplantation. It was hypothesized that poor child HRQOL, poor child and parent psychological functioning and disrupted family functioning would be associated with nonadherence, and that increased rates of nonadherence would be related to poor health outcomes.

Materials and Method

Participants

This protocol was approved by the Institutional Review Board of the University of Michigan Medical School. Participants were recruited from the Pediatric Liver Transplant Clinic at the University of Michigan. All children between the ages of 2–16 years, who were within 5 years of liver transplantation, were eligible for participation if at least one parent/guardian was fluent in English. Potential participants were identified by searching the clinical database of the Organ Transplantation Information System at the University of Michigan. Forty-five eligible participants were identified and were recruited by mail and/or face-to-face contact during their clinic visit. Of the eligible participants contacted, 38 (84%) agreed to participate. Seven families declined participation due to time constraints and/or the presence of other children at the clinic visit.

Procedures

Parent/guardian(s) and children (≥6 years old, n = 23) completed empirically based, standardized assessment measures following their regularly scheduled Pediatric Liver Transplant Clinic appointment. This assessment battery evaluated HRQOL, parent and child psychological functioning and family functioning using instruments considered to be the gold standard for measuring these constructs (Table 2). The assessment battery was administered by a pediatric psychologist (EMF), and questionnaires were reviewed upon completion. Any parent or child who endorsed critical items or significant symptoms of a mental health disorder underwent an interview with the psychologist, and were offered assistance in locating mental health services. Measures of regimen adherence and health status were also obtained from the child's medical records. Families were reimbursed for their time and effort devoted to study-related activities.

Measures

HRQOL: Pediatric Quality of Life Inventory-Generic Core Scales (PedsQL4.0 (14): The PedsQL is a well-validated modular instrument for measuring HRQOL in children and adolescents. The PedsQL4.0 Core Scales is a 23-item inventory that assesses physical, emotional, social and school functioning. Parent-proxy report of HRQOL was measured for all participants, and pediatric self-report was measured in children and adolescents older than 6 years. Higher scores on this measure are indicative of more positive HRQOL.

Child Health Questionnaire-Parent Form 50 (CHQ-PF50© (15): The CHQ-PF50 is a 50-item empirically validated questionnaire completed by a parent/caregiver. The instrument assesses a broad spectrum of child- and family-focused health areas. Higher scores on this measure are indicative of more positive health status.

Child psychological functioning: Child Behavior Checklist Parent Report Form (CBCL/11/2–5, CBCL/6–18 (16,17). The CBCL forms are standardized parent-report measures of behavioral problems and social competencies of children. The CBCL/11/2 to 5 years is scored for Internalizing, Externalizing and Total Problems and 7 syndromes. The CBCL/6–18 years is scored for three competence scales (Activities, Social and School), Total Competence, three summary scales (Internalizing, Externalizing and Total Problems), eight empirically derived syndromes scales, and six DSM-oriented scales. In this study, only scales that appear on both forms were used. High scores on the summary, syndrome and DSM-oriented scales (T ≥ 63, 90th percentile) are indicative of clinically significant disturbances, while low scores on the

Table 2: Psychological and HRQOL assessment measures

Measure	Scales used in present study	Sample question(s)
Pediatric Quality of Life Inventory-Generic Core Scales (PedsQL4.0) (14)	Total functioning Physical functioning Emotional functioning Social functioning School functioning	Items are rated on a 5-point Likert scale 'In the last month, how much trouble have you (has your child) had with . . .' • Participating in sports activity or exercise • Feeling sad or blue • Keeping up with schoolwork
Child Health Questionnaire-Parent Form 50 (CHQ-PF50©) (15)	Physical functioning General health Role/social limitations—emotional, behavioral Role/social limitations —physical Bodily pain Behavior Mental health Self-esteem Parent impact—time Parent impact—emotional Family activities Family cohesion Total—physical Total—psychosocial Total—psychosocial	Items are rated on a Likert scale (4–6 point depending on subscale) • Has your child's school work or activities with friends been limited in any of the following ways due to emotional difficulties or problems with his/her behavior – limited in the kind of schoolwork or activities with friends he/she could do; limited in the amount of time he/she could spend on schoolwork or activities with friends; limited in performing schoolwork or activities with friends? • How much of the time do you think your child: felt like crying; felt lonely; acted nervous; bothered or upset; cheerful? • How much emotional worry or concern did each of the following cause you – your child's physical health; emotional well-being or behavior; attention or learning abilities?
Child Behavior Checklist Parent Report Form (CBCL) (16,17)	Internalizing, externalizing and total problems Competency scales: *Activities* *Social* *School* Clinical syndrome scales: *Aggressive behavior* *Anxious/Depressed* *Attention problems* *Social problems* *Withdrawn/Depressed*. DSM-oriented scales: *Affective problems* *Anxiety problems* *Attention deficit hyperactivity problems* *Oppositional defiant problems* *Conduct problems*	Items are rated on a 3-point scale • Argues a lot • Can't concentrate • Too fearful or anxious • Unhappy, sad, depressed • Doesn't get along with other kids
Brief Symptom Inventory (BSI) (18)	Global Severity Index	Respondents rate the perceived severity of 53 psychological and physical symptoms on a 5-point scale ranging from 0 ('not at all') to 4 ('extremely') • Feeling tearful • Trouble remembering things • Feeling tense or keyed up
Beck Depression Inventory (BSI) (19)	Global depression	23 items are rated on a 4-point scale • Sadness • Pessimism • Guilty feelings • Crying • Self-dislike

Continued.

Table 2: Continued

Measure	Scales used in present study	Sample question(s)
Pediatric Inventory for Parents (PIP) (20)	Communication Emotional functioning Medical care Role functioning Total frequency Total difficulty	Items are rated on a 5-point Likert Scale 'How often has the event occurred for you in the past 7 days, and how difficult it was/or generally is for you' • Difficulty sleeping • Arguing with family members • Feeling confused about medical information • Being with my child during medical procedures
Family Assessment Device (FAD) (21)	Problem solving Communication Roles Affective responsiveness Affective involvement Behavior control General functioning	Items are rated on a 4-point Likert scale from 1 (strongly agree) to 4 (strongly disagree) • We resolve most everyday problems around the house • We confront problems involving feelings • Planning family activities is difficult because we misunderstand each other
Family Environment Scale (FES) (22)	Cohesion Conflict	Items are scored as True or False • Family members often keep their feelings to themselves • Family members hardly ever lose their tempers • We really get along well with each other • We fight a lot in our family

competence scales (T < 37, <10th percentile) are indicative of functioning in the clinically significant range.

Parent psychological functioning: Brief Symptom Inventory (18): Parents completed the BSI, which is an abbreviated 53-item version of the Symptom Checklist-90-Revised that assesses nine clinical dimensions of psychological distress, and yields a Global Severity Index (GSI) used to assess overall distress. Only the Global Severity Index was used in these analyses.

Beck Depression Inventory (19): Parents completed the BDI-II, which is a 21-item self-report measure used to assess depressive symptomatology.

Pediatric Inventory for Parents (20): Parents completed the PIP, which is a 42-item measure of stress related to parenting a child with a chronic illness. Items are grouped into four domain scales: Communication, Emotional Functioning, Medical Care and Role Functioning. Parents rate each item as to the item's frequency over the past week and the level of difficulty associated with it. Scale scores are combined for Total Frequency and Total Difficulty scores. Higher scores indicate greater frequency and greater difficulty.

Family functioning: Family Assessment Device (21): Parents completed the FAD, which is a 60-item self-report measure that describes structural and organizational properties of the family and patterns of transaction among family members. The FAD provides scores for six domains of family functioning. Scaled scores range from 0 to 4 with a clinical cutoff of 2 (i.e. scores of 2 or more indicate unhealthy functioning).

Family Environment Scale (22): Parents completed the Cohesion and Conflict subscales of the FES. These subscales assess the extent to which family members are helpful, supportive and committed to one another, and the extent to which conflictual interactions are characteristic of the family.

Adherence behaviors: Regimen adherence was evaluated retrospectively using multiple indices. Definitions of adherence were determined using stringent cut-offs based on previous research showing that minimal deviations from dosing schedule of the immunosuppressive regimens were associated with an increase risk of poor clinical outcomes (23,24).

Clinic Attendance Adherence to clinic visits was assessed by comparing clinic attendance to the number and interval frequency recommended by the transplant team. The rate of clinic attendance was obtained from the child's medical record. Adherence was defined as a clinic attendance rate of ≥80%.This definition is consistent with the pediatric adherence literature (25).

Immunosuppressant Levels To measure adherence to post-transplant immunosuppressant medications, data from routine monitoring of tacrolimus blood levels were obtained from the child's medical record. Tacrolimus levels obtained during inpatient hospitalization stays were not included in the analyses. Standard deviations (SDs) of consecutive trough tacrolimus blood levels were calculated. Shemesh and colleagues have demonstrated the predictive and concurrent validity of the use of SD of tacrolimus blood levels as a measure of adherence to immunosuppressive medications (26). Specifically, higher fluctuations have been used as an indicator of variable medication administration, and tacrolimus SD was significantly related to clinician ratings of nonadherence, as well as health outcome including episodes of rejection (26). In this study, adherence was defined as an SD <2.5.

Health status: Measures of child health status including graft function, frequency of hospital admissions, liver biopsies and episodes of rejection for the year prior to study participation were collected via patient medical records.

Statistical method

Sample mean subscale and summary scores obtained on the psychological measures were compared with published normative data for healthy children and data from other pediatric chronic illness populations when published norms were available using two-tailed *t*-tests. Correlations were used to identify the relationships between scores on the psychosocial measures and measures of post-transplant adherence and health outcomes. Pearson's product moment correlation coefficients were calculated whenever the assumptions underlying parametric statistical testing were met. However, if study measures exhibited frequency distributions which differed from the normal distribution, Spearman's rank correlation coefficient were used instead. Participants were categorized as 'adherent' or 'nonadherent' based on their rate of clinic attendance and tacrolimus SD. Two-sample *t*-tests were used to assess differences between 'adherent' and 'nonadherent'

Table 3: Participant demographics

Factor	Mean ± SD
Maternal age (years)	37.0 ± 7.8
Paternal age (years)	40.3 ± 6.8
Child's age (months)	102.0 ± 44.7
Time since transplant (months)	25.2 ± 17.7
Child gender	Female = 20 (51.6%)
	Male = 18 (47.4%)
Child race (parent-reported)	White (57.9%)
	African American (31.6%)
	Native American (2.6%)
	Hispanic (2.6%)
	Multiracial (2.6%)
	Other (2.6%)
Diagnosis	Biliary atresia (44.7%)
	Fulminant hepatic failure (15.8%)
	Autoimmune hepatitis (13.2%)
	Hepatoblastoma (7.9%)
	Hepatitis (5.3%)
	Sclerosing cholangitis (5.3%)
	Alpha-1 antitrypsin (2.6%)
	Argininosuccinic aciduria (2.6%)
	Byler's syndrome (2.6%)

participants with respect to the behavioral health measures, and health outcomes. All analyses were conducted using the SPSS version 13.0 statistical package.

Results

Demographics

Participants included 38 children (Mean = 8.5 years, range 28 months to 16 years) who were within 5 years of liver transplantation (Mean time since transplant = 25.2 months, range 1–64 months) and their parent/guardian(s). Ninety percent of parent respondents were mothers. Clinical and demographic information is provided in Table 3. There were significant relationships between child age and measures of parenting stress (PIP-F, $r = -0.38$, $p = 0.019$; PIP-D, $r = -0.41$, $p = 0.001$), and tacrolimus SD ($r = -0.37$, $p = 0.038$). Thus, all subsequent analyses controlled for the effects of age. There were no significant relationships between time since transplantation, race or other demographic variables and measures of psychosocial functioning, adherence or health status.

HRQOL

Based on parent proxy-reports on the PedsQL4.0, the mean scores for total functioning, physical and psychosocial health, emotional, social and school functioning were all significantly lower in LT recipients as compared to published norms for healthy children ($p = 0.0001$; See Table 4). LT recipients had significantly lower school functioning compared to normative data for children with cancer ($p = 0.012$) and diabetes ($p = 0.0001$), and also had significantly lower mean scores for total functioning ($p = 0.0001$), physical functioning ($p = 0.001$), psychosocial health ($p = 0.004$) and social functioning ($p = 0.005$) compared to children with diabetes.

Child self-reports on the PedsQL4.0 suggest that mean scores for total functioning ($p = 0.001$), physical ($p = 0.008$), psychosocial health ($p = 0.002$), social ($p = 0.006$) and school functioning ($p = 0.0001$) were significantly lower in LT recipients as compared to published norms for healthy children. Consistent with parental report, LT recipients reported significantly lower school functioning than children with cancer ($p = 0.049$) and diabetes ($p = 0.003$). They also reported significantly lower total ($p = 0.007$), physical ($p = 0.004$), psychosocial ($p = 0.041$), social ($p = 0.015$) and school functioning ($p = 0.003$) than normative data for children with diabetes.

Table 4: PedsQL 4.0 parent proxy-report and child self-report for liver transplant recipients and comparisons with healthy children, and children with chronic illness

	Liver transplant		Healthy*			Cancer*			Diabetes*		
Scale	n	Mean ± SD	n	Mean ± SD	p-Value	n	Mean ± SD	p-Value	n	Mean ± SD	p-Value
Parent proxy report											
Total score	38	65.00 ± 18.62	717	87.61 ± 12.33	0.0001	336	69.70 ± 19.17	ns	307	76.56 ± 14.10	0.0001
Physical health	38	64.97 ± 28.28	717	89.32 ± 16.35	0.0001	336	68.75 ± 24.98	ns	307	81.99 ± 17.22	0.001
Psychosocial health	38	64.76 ± 17.63	717	86.58 ± 12.79	0.0001	336	70.31 ± 17.96	ns	307	73.61 ± 15.37	0.004
Emotional functioning	38	66.32 ± 21.89	718	82.64 ± 17.54	0.0001	336	67.53 ± 20.32	ns	307	69.08 ± 18.57	ns
Social functioning	38	70.79 ± 21.01	716	91.56 ± 14.20	0.0001	336	75.64 ± 20.61	ns	305	81.03 ± 19.38	0.005
School functioning	38	56.63 ± 21.73	611	85.47 ± 17.61	0.0001	250	66.40 ± 23.19	0.012	299	70.8 ± 19.39	0.0001
Child self-report											
Total score	23	69.82 ± 17.15	401	83.00 ± 14.79	0.001	219	72.20 ± 16.38	ns	300	80.37 ± 12.90	0.007
Physical health	23	69.46 ± 24.52	400	84.41 ± 17.26	0.008	219	71.79 ± 21.80	ns	300	85.95 ± 13.34	0.004
Psychosocial health	23	69.47 ± 16.94	399	82.38 ± 15.51	0.002	219	72.62 ± 16.41	ns	300	77.34 ± 14.62	0.041
Emotional functioning	23	76.52 ± 20.53	400	80.86 ± 19.64	ns	219	71.83 ± 21.44	ns	300	72.37 ± 19.57	ns
Social functioning	23	74.35 ± 20.52	399	87.42 ± 17.18	0.006	219	76.84 ± 20.31	ns	300	85.63 ± 16.24	0.015
School functioning	23	58.91 ± 22.05	386	78.63 ± 20.53	0.0001	191	68.51 ± 19.72	0.049	297	74.2 ± 18.08	0.003

*Data for healthy children and children with chronic illness were retrieved from published references (29, 30).
NOTE: Scores range from 0 to 100, with higher scores reflecting better HRQOL.

Table 5: CHQ-PF50 Summary scores for liver transplant recipients compared to normative data for healthy population

Scales	Liver transplant mean ± SD	Healthy* mean ± SD	Significance
Physical functioning	68.8 ± 34.9	96.1 ± 13.9	p = 0.0001
Role/Social–Emotional, behavioral	70.2 ± 32.3	92.5 ± 18.6	p = 0.0001
Role/Social–Physical	73.0 ± 37.5	93.6 ± 18.6	p = 0.002
Bodily pain	70.0 ± 28.9	81.7 ± 19.0	p = 0.017
General behavior	65.6 ± 21.0	75.6 ± 16.7	p = 0.006
Mental health	72.3 ± 13.5	78.5 ± 13.2	p = 0.008
Self esteem	75.4 ± 18.7	79.8 ± 17.5	p = 0.160
General health perceptions	43.1 ± 16.6	73.0 ± 17.3	p = 0.0001
Parental impact–time	58.3 ± 33.8	87.8 ± 19.9	p = 0.0001
Parental impact–emotional	46.9 ± 31.3	80.3 ± 17.3	p = 0.0001
Family activities	64.6 ± 24.6	89.7 ± 18.6	p = 0.0001
Family cohesion	71.1 ± 22.5	72.3 ± 8.8	p = 0.743
Physical functioning summary	36.4 ± 17.3	53.0 ± 8.8	p = 0.0001
Psychosocial functioning summary	43.7 ± 11.0	51.2 ± 9.1	p = 0.0001

Note: Individual scores range from 0 to 100, with higher scores reflecting better HRQOL.
*Data for healthy population were retrieved from published references (15)

Table 5 presents means and standard deviations for the subscales of the CHQ-PF50 for LT recipients compared with healthy children population scores (15). Results from the CHQ-PF50 indicate that physical and psychosocial summary scores were significantly lower for LT recipients than for the general population (p = 0.0001). Compared to the general population, LT recipients had significantly lower scores on individual subscales including physical functioning (p = 0.0001), role/social limitations-emotional/behavioral (p = 0.0001), role/social limitations-physical (p = 0.002), bodily pain (p = 0.017), general behavior (p = 0.006), mental health (p = 0.008) and general health perceptions (p = 0.0001).

Child psychological functioning

Parent reports on the CBCL indicated that aggregate scores on the summary scales (Total Problems, Internalizing Problems, Externalizing Problems) for the LT group as a whole were not clinically elevated, and with the exception of Internalizing Problems (p = 0.029), the Total and Externalizing Problems scales did not differ significantly from norms for healthy children. Aggregate scores for CBCL subscales were not in the clinically significant range, but they did differ significantly from norms for healthy children (see Table 6). Further analyses of the CBCL results revealed that compared to normative data for healthy children, wherein 7% were in the clinical range on summary scales and subscales (16), a disproportionate number of LT recipients exceeded clinical cutoffs on all summary scales and subscales (Table 6). Compared to 25–30% of children in the normative sample, 60.5% of LT recipients were within the clinical range on Internalizing and/or Externalizing, Total Problems and at least one clinical subscale.

Parent psychological functioning

Global measures of parent functioning (BDI-II, BSI) were within the normal range and did not differ significantly from normative data for the general population. Parent reports on subscales of the CHQ-PF50 that assess parent functioning related to child HRQOL indicated that parents of LT recipients reported a greater impact on time (p = 0.0001) and emotions (p = 0.0001) than parents of children in the general population (Table 5). With regard to parenting stress, parents of LT recipients reported significantly higher scores on the PIP Total-Frequency (p = 0.029) and Total-Difficulty scales (p = 0.025) than parents of children with type 1 diabetes, but reported comparable Total-Frequency scores (p = 0.22), and significantly lower scores on the Total-Difficulty scale (p = 0.0001) than parents of children with cancer.

Family functioning

On the CHQ-PF50 family activities subscale, parents reported significantly lower scores than norms for the general population (p = 0.0001), though scores for family cohesion were similar (Table 5). On the FAD, no significant differences were found between families of LT recipients and published norms for nonclinical families or families with medically ill members. Likewise, on the FES, no significant differences were found between families of LT recipients and published norms for the general population.

Adherence behavior

Participants had an average of 7.54 ± 6.2 blood levels of tacrolimus in the year prior to study participation (range 1–27). The mean tacrolimus SD was 3.15 ± 3.3 ng/mL (range 0.38–19.30 ng/mL). Participants attended an average of 78.7 ± 18.3% of scheduled clinic visits (range 37.5–100%). There was no significant relationship between tacrolimus SD and the rate of clinic attendance, suggesting that these measures assess different aspects of regimen adherence. As such, participants were classified categorically as 'adherent' and 'nonadherent' with respect to tacrolimus SD and rate of clinic attendance. Forty-two percent (n = 16) of participants were classified as nonadherent based on tacrolimus SD > 2.5, and 50% (n = 19) were nonadherent based on a rate of clinic attendance of <80%.

Table 6: CBCL summary, subscale and competency scales compared to normative sample

	LT recipients Mean ± SD	Compared to normative sample (T = 50)	Percent of LT recipients exceeding clinical cutoffs*
Anxious/depressed	55.62 ± 7.30	p = 0.0001	27
Withdrawn/depressed	55.65 ± 6.70	p = 0.0001	21.6
Somatic complaints	57.76 ± 7.28	p = 0.0001	24.3
Social problems	56.46 ± 7.16	p = 0.0001	25
Thought problems	57.93 ± 8.17	p = 0.0001	35
Attention problems	57.19 ± 8.55	p = 0.0001	18.9
Rule breaking behavior	55.11 ± 6.6	p = 0.0001	17.8
Aggressive behavior	55.84 ± 8.15	p = 0.0001	18.9
DSM-IV affective problems	58.11 ± 7.91	p = 0.0001	32.4
DSM-IV anxiety problems	56.27 ± 7.56	p = 0.0001	29.7
DSM-IV somatic problems	57.39 ± 7.37	p = 0.0001	25
DSM-IV ADHD	55.90 ± 6.87	p = 0.0001	18.9
DSM-IV oppositional defiant	55.24 ± 6.57	p = 0.0001	16.2
DSM-IV conduct problems	55.71 ± 7.35	p = 0.0001	21.4
Total problems	52.97 ± 12.66	p = 0.162	32.4
Internalizing problems	53.89 ± 10.40	p = 0.029	21.6
Externalizing problems	50.92 ± 12.23	p = 0.650	18.9
Activity competency	41.04 ± 10.38	p = 0.0001	35.7
Social competency	41.73 ± 10.42	p = 0.0001	34.6
School competency	40.22 ± 8.85	p = 0.0001	39

*NOTE: 7% of the normative sample exceeds clinical cutoffs of T > 63 on summary and clinical subscales, and T < 37 on competency scales (16).

Health status

Within the 12 months prior to participation, 26.3% of the participants had been hospitalized at least once, 18.4% underwent at least one liver biopsy and 10.5% had a documented biopsy-proven episode of rejection. There were 22 hospital admissions, 96 inpatient days, 7 liver biopsies and 4 biopsy-proven episodes of rejection. At the time of participation, 3 participants had evidence of graft dysfunction as defined by total bilirubin >2. Two of these three participants had documented nonadherence that led to graft dysfunction, and one participant had severe graft dysfunction of unknown etiology. Two participants had percutaneous transhepatic cholangiography (PTC) tubes at the time of participation for biliary strictures.

Relationship between child, parent and family functioning and adherence behavior

The distribution of the tacrolimus SD values significantly deviated from normal, thus nonparametric Spearman correlations were conducted to examine relationships with psychosocial and health outcome measures.

Correlations with HRQOL and behavioral functioning: Tacrolimus SD was not significantly related to measures of child HRQOL or behavioral functioning. The rate of clinic attendance was significantly related to parent-proxy reports of child physical HRQOL (CHQ-PF50, r = 0.36, p = 0.045). These associations remained significant after controlling for a child's age and the time since transplantation.

Correlations with parent functioning: Tacrolimus SD was significantly related to impact on parent emotional functioning as it relates to their child's status (CHQ-PF50, rho = –0.341, p = 0.042). The rate of clinic attendance was significantly associated with overall illness-related parenting stress as measured by the PIP, including the difficulty of stressful events related to the child's medical care (r = –0.41, p = 0.017), communication with the child and healthcare team (r = –0.39, p = 0.23) and role functioning (r = –0.44, p = 0.008). These associations remained significant after controlling for a child's age and the time since transplantation.

Correlations with family functioning: Tacrolimus SD was not significantly related to measures of family functioning. The rate of clinic attendance was significantly related to family cohesion (CHQ-PF50, r = 0.46, p = 0.009) and family problem-solving (FAD, r = 0.41, p = 0.021).

Relationship between adherence behaviors and health outcomes

Tacrolimus SD was significantly correlated with the frequency of hospital admissions (rho = 0.47, p = 0.004), duration of hospitalizations (rho = 0.39, p = 0.02), and liver biopsies (rho = 0.34, p = 0.043). The rate of clinic attendance was significantly correlated with hospital admissions (r = –0.51, p = 0.001), duration of hospitalization (r = –0.511, p = 0.001), liver biopsies (r = –0.42, p = 0.01), and rejection episodes (r = –0.36, p = 0.026).

Differences between 'adherent' and 'nonadherent' participants

Table 7 provides a summary of the differences between adherent and nonadherent group with respect to child, parent, family and health outcome variables.

Table 7: Comparison of adherent vs. nonadherent participants

	Tacrolimus SD			Rate of Clinic Attendance		
Factor	Nonadherent (mean ± SD)	Adherent (mean ± SD)	p-Value	Nonadherent (mean ± SD)	Adherent (mean ± SD)	p-Value
CHQ-PF50 Parent Impact-Emotional	32.29 ± 31.16	57.54 ± 28.0	p = 0.014	–	–	n.s
CHQ-PF50 Family cohesion	61.9 ± 28.2	77.7 ± 14.1	p = 0.035	61.3 ± 24.3	81.4 ± 14.9	p = 0.005
CHQ-PF50 Role/Social limitations, Emotional-Behavioral	60.7 ± 33.8	81.3 ± 24.6	p = 0.048	–	–	n.s.
PIP Role functioning	–	–	n.s.	25.5 ± 6.8	20.7 ± 5.9	p = 0.028
Hospital admissions	1.19 ± 1.86 (total = 77)	0.14 ± 0.36 (total = 19)	p = 0.017	1.00 ± 1.76 (total = 89)	0.16 ± 0.37 (total = 7)	p = 0.049
Liver biopsies	0.44 ± 0.62 Total = 7	0.19 ± 0.40 Total = 1	p = 0.012	0.32 ± 0.59 Total = 6	0.11 ± 0.31 Total = 2	n.s.
Rejection episodes	0.19 ± 0.40 Total = 3	0.04 ± 0.22 Total = 1	n.s	0.21 ± 0.42 Total = 4	0	p = 0.035

Tacrolimus SD: Compared to parents in the adherent group, parents in the nonadherent group reported a greater impact on their emotional functioning (CHQ-PF50, p = 0.014), and significantly lower family cohesion (CHQ-PF50, p = 0.035). Moreover, parents in the nonadherent group reported that their children had significantly more role/social limitations as a result of emotional/behavioral difficulties (CHQ-PF50; p = 0.048). Participants in the nonadherent group had significantly more hospital admissions (p = 0.017) and liver biopsies (p = 0.012) than the adherent group.

Rate of clinic attendance: Compared to parents in the adherent group, parents in the nonadherent group reported more stress related to role functioning (PIP, p = 0.028), and significantly lower family cohesion (CHQ-PF50, p = 0.005). There were no between-group differences with respect to child HRQOL or behavioral functioning. Participants in the nonadherent group had significantly more hospital admissions (p = 0.049) and rejection episodes (p = 0.035) than the adherent group.

Discussion

Previous research with other pediatric chronic illness groups have documented the link between child behavior problems, parental psychological distress, family distress and regimen nonadherence (11,13,27). Yet, the relationship between these variables and post-transplant adherence among pediatric LT recipients has not been investigated. Given the severe consequences associated with nonadherence, the current study aimed to use empirically sound psychological assessment measures to identify correlates of nonadherence which could be targeted in an intervention to improve adherence and clinical outcomes. It was hypothesized that poor child HRQOL, poor parent and child psychological functioning and disrupted family functioning would be associated with nonadherence, and increased rates of nonadherence would be related to poor health outcomes. Results of the current study supported these hypotheses. Specifically, nonadherence was related to lower physical HRQOL, more limitations in social and school activities related to emotional and behavioral problems, greater impact on parental emotional functioning, and decreased family cohesion. Moreover, nonadherence was related to frequency and duration of hospitalizations, liver biopsies and rejection episodes.

In the current study, rates of nonadherence ranged from 42% to 50%. These rates are striking, and are consistent with estimates of rates of nonadherence with medical regimens among general pediatric (5,13) and pediatric LT populations (3,4). With respect to the relationship between adherence and health outcomes, tacrolimus SD was significantly related to the number of hospital admissions, duration of hospitalizations and liver biopsies. The rate of clinic attendance was significantly correlated with hospital admissions, duration of hospitalization, liver biopsies and rejection episodes. There continues to be a lack of a gold standard with respect to measuring adherence to prescribed post-transplant medical regimens. Electronic medication monitoring technology, such as the Medication Event Monitoring System (MEMS®; Aprex Corporation, Union City, CA), is considered to be the recommended measure in adherence research; however, this technology has not been well studied in pediatric transplant populations. Moreover, there are barriers associated with the MEMS technology including cost, the inability to use with liquid medications, and the possibility that these devices may interfere with established adherence routines, such as the use of pillbox organizers. Indeed, this current study proposed the use of MEMS caps, but only three families consented to their use. Data on these three families were not reported due to the small sample size. The majority of families cited barriers including use of liquid medication, the size of the MEMS TrackCap and the potential disruption of their existing organizational system.

Shemesh and colleagues found that tacrolimus SD were predictive of health outcomes such as liver biopsies and episodes of rejection (10,11). Thus, they concluded that

tacrolimus SDs were fairly specific predictors of clinically relevant nonadherence rather than nonspecific predictors of poor outcome. The current study failed to find a relationship between tacrolimus blood levels and documented episodes of rejection. One possible explanation could be the small sample size and infrequent occurrence of rejection within the current sample. Yet, this also raises the question as to whether tacrolimus SD is a valid and reliable technique to measure adherence behavior. Further study examining reliable and valid measures of regimen adherence in pediatric transplantation is warranted.

The results of the present study extended previous work by demonstrating that within the first 5 years following transplant, parent-proxy and child self-reports indicate that the HRQOL of LT recipients is adversely affected in all areas of functioning when compared with normative data for healthy children, and was impaired with respect to school functioning when compared to children with other chronic illnesses. The convergence between parent and child reports of HRQOL was striking, and clearly strengthens the findings of this study. Moreover, study participants had a disproportionately higher level of attention, conduct and emotional problems compared to the general population, and evidenced poor competencies in life activities, social function and school. More than half of the participants were in the clinically significant range on at least one area of problem behavior. Yet, despite reports of decreased HRQOL, increased behavioral/emotional problems and decreased competencies, there were few significant relationships with measure of adherence.

Though there was the lack of significance between most measures of child functioning and adherence, it is possible that children who experience high rates of problematic behavior may cause their parents and family to experience high levels of stress. Alternatively, high rates of parental stress may be associated with inconsistent parenting styles which may exacerbate child behavior problems and family conflict. Moreover, both children and parents may be negatively impacted by the child's medical condition. Thus, although most measures of child HRQOL and behavior problems were not significantly related to adherence, it is important to focus on child functioning given the impact on parent and family functioning. Further, little is known regarding the long-term impact of such behavior problems on adherence.

It is widely accepted that parenting a chronically ill child is taxing emotionally, socially and financially. However, the relationship between parenting stress and health outcomes among pediatric transplant recipients is not well understood. Intervening at the parent and family level may lead to improved health outcomes; yet, before interventions can be developed, we need a better understanding of the relationship between parent and family functioning and health outcomes. In the present study, parenting stress and family cohesiveness were significantly related to measures of adherence behavior. Specifically, parents of LT recipients reported a greater impact on time and emotions than did parents of children in the general population, and reported a high level of stress related to caring for a child with a medical condition. Parenting stress was significantly related to poor adherence. Likewise, the extent to which family members get along with each other was also related to adherence. These findings are consistent with research investigating correlates of nonadherence with other pediatric chronic illness groups (13).

The current study was limited by its small sample size and single transplant center. Moreover, though the participants were homogeneous with respect to time since transplant (i.e. within 5 years), the sample was heterogeneous with respect to age and diagnosis. This may further impact adherence and HRQOL. In addition, there may have been a selection bias present wherein patients and families who are nonadherent did not participate. This selection bias is present in many studies investigating regimen adherence (5). The retrospective, cross-sectional nature of this study also precludes us from making conclusions regarding causality. The current study reports the association between parent and family stress, and poor health outcomes (i.e. rejection), but the direction of these relationships remain unclear. It is likely that parent and family stress is multifactorial related to the child's health status, as well as other environmental or pre-existing factors, such as socioeconomic status. Prospective longitudinal studies are required to identify impact of child, parent and family functioning on adherence and health outcomes.

Despite limitations, this study has significant clinical implications. Nonadherence was significantly related to aspects of parenting stress and family cohesiveness. Empirically based assessment of modifiable factors will help identify patients at risk for nonadherence, and may allow for the appropriate delivery of interventions to ameliorate this risk. Interventions should not only directly target adherence behaviors such as pill taking and clinic attendance, but should also focus on parent and family variables as these factors were significantly related to nonadherence rates. Specifically, future interventions should target parent coping, communication, stress management, and support in daily roles and responsibilities.

Acknowledgment

This work was funded by CS Mott Children's Hospital and Division of General Pediatrics, University of Michigan Medical School.

References

1. Sudan DL, Shaw BW, Jr., Langnas AN. Causes of late mortality in pediatric liver transplant recipients. Ann Surg 1998; 227: 289–295.
2. Molmenti E, Mazariegos G, Bueno J et al. Noncompliance after pediatric liver transplantation. Transplant Proc 1999; 31: 408.

3. Lurie S, Shemesh E, Sheiner PA et al. Non-adherence in pediatric liver transplant recipients–an assessment of risk factors and natural history. Pediatr Transplant 2000; 4: 200–206.
4. Falkenstein K, Flynn L, Kirkpatrick B, Casa-Melley A, Dunn S. Noncompliance in children post-liver transplant. Who are the culprits? Pediatr Transplant 2004; 8: 233–236.
5. LaGreca AM, Schuman WB. Adherence to prescribed medical regimens. In: Roberts M, editor. Handbook of Pediatric Psychology: Guilford Press; 1995: 55–83.
6. Taylor R, Franck LS, Gibson F, Dhawan A. A critical review of the health-related quality of life of children and adolescents after liver transplantation. Liver Transpl 2005; 11: 51–60; discussion 7–9.
7. Bucuvalas JC, Britto M, Krug S et al. Health-related quality of life in pediatric liver transplant recipients: A single-center study. Liver Transpl 2003; 9: 62–71.
8. Alonso EM, Neighbors K, Mattson C et al. Functional outcomes of pediatric liver transplantation. J Pediatr Gastroenterol Nutr 2003; 37: 155–160.
9. Midgley DE, Bradlee TA, Donohoe C, Kent KP, Alonso EM. Health-related quality of life in long-term survivors of pediatric liver transplantation. Liver Transpl 2000; 6: 333–339.
10. Shemesh E. Non-adherence to medications following pediatric liver transplantation. Pediatr Transplant 2004; 8: 600–605.
11. Shemesh E, Lurie S, Stuber ML et al. A pilot study of posttraumatic stress and nonadherence in pediatric liver transplant recipients. Pediatrics 2000; 105: E29.
12. Young GS, Mintzer LL, Seacord D, Castaneda M, Mesrkhani V, Stuber ML. Symptoms of posttraumatic stress disorder in parents of transplant recipients: Incidence, severity, and related factors. Pediatrics 2003; 111(6 Pt 1): e725–31.
13. Lemanek KL, Kamps J, Chung NB. Empirically supported treatments in pediatric psychology: Regimen adherence. J Pediatr Psychol 2001; 26: 253–275.
14. 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.
15. Landgraf JL AL, Ware JE. The CHQ User's Manual. Boston, NE: The Health Institute, New England Medical Center; 1996.
16. Achenbach TM, Rescorla LA. Manual for ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2001.
17. Achenbach TM, Rescorla LA. Manual for ASEBA Preschool Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2000.
18. Derogatis LR. Brief symptom inventory. Minneapolis, MN: National Computer Systems, Inc.; 1993.
19. Beck AT, Steer RA, Brown GK. Beck Depression Inventory-II manual. San Antonio, TX: Psychological Corp; 1996.
20. Streisand R, Braniecki S, Tercyak KP, Kazak AE. Childhood illness-related parenting stress: The pediatric inventory for parents. J Pediatr Psychol 2001; 26: 155–162.
21. Epstein NB, Baldwin L, Bishop DS. The McMaster family assessment device. J Marital Fam Ther 1983; 9: 171–180.
22. Moos R, Moos B. *Family environment scale manual*. 2nd ed. Palo Alto, CA: Consulting Psychologists Press; 1986.
23. De Geest S, Abraham I, Moons P, Vandeputte M, Van Cleemput J, Evers G, et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. J Heart Lung Transplant 1998; 17: 854–863.
24. Nevins TE, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. Kidney Int 2001; 60: 1565–1570.
25. Rapoff MA. Adherence to pediatric medical regimens. New York: Kluwer Academic/Plenum Press; 1999.
26. Shemesh E, Shneider BL, Savitzky JK et al. Medication adherence in pediatric and adolescent liver transplant recipients. Pediatrics 2004; 113: 825–832.
27. Gerson AC, Furth SL, Neu AM, Fivush BA. Assessing associations between medication adherence and potentially modifiable psychosocial variables in pediatric kidney transplant recipients and their families. Pediatr Transplant 2004; 8: 543–550.
28. World Health Organization. Constitution of the World Health Organization: Chronicle of the World Health Organization 1.: Geneva: WHO; 1947.
29. Varni JW, Burwinkle TM, Jacobs JR, Gottschalk M, Kaufman F, Jones KL. The PedsQL in type 1 and type 2 diabetes: Reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales and type 1 Diabetes Module. Diabetes Care 2003; 26: 631–637.
30. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer 2002; 94: 2090–2106.