Childhood Abuse, Nonadherence, and Medical Outcome in Pediatric Liver Transplant Recipients

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ABSTRACT

Objective: The study assessed the relationship between a history of child abuse, nonadherence to medications, and medical outcome in children who had a liver transplant. **Method:** Abuse history for children and adolescents ages 8 to 21 who underwent a liver transplantation at Mount Sinai Medical Center in New York was obtained in interviews in 2002. Adherence to tacrolimus was assessed from January 1 to December 31, 2003 by computing the SD of a series of medication blood levels for each patient. Biopsy-proven rejection episodes, degree of fluctuation of alanine aminotransferase (ALT), and maximal ALT levels were recorded as indicators of medical outcome. **Results:** Of 72 eligible patients, 56 were evaluated. Five had documented abuse. Abused children were less adherent to their medication regimen ($p = .02$; 95% confidence interval [CI] -2.66 to -0.24), had poor disease control (higher maximal ALT, $p < .01$; 95% CI -613.72 to -249.55), had greater fluctuation in ALT levels ($p < .01$; 95% CI -151.19 to -65.91), and suffered more biopsy-proven rejection episodes (two episodes in the abused cohort versus none in the rest) in 2003. **Conclusions:** A history of child abuse is a significant risk factor for poor outcome posttransplantation and should be evaluated routinely. Adherence to medications can be a target for intervention in patients with a history of abuse. *J. Am. Acad. Child Adolesc. Psychiatry,* 2007;46(10):1280–1289. **Key Words:** nonadherence, abuse, domestic violence, liver transplant.

Psychosocial evaluations are an integral part of the routine pretransplantation evaluation procedure for solid organ transplant recipients (Dew et al., 2000; European Expert Group on Renal Transplantation, 2000, 2002; Levenson and Olbrisch, 1993; Olbrisch and Levenson, 1995; Olbrisch et al., 2002; Skotzko et al., 2001). Prospective longitudinal studies are needed to identify specific risks that should be focused on in these evaluations (Olbrisch and Levenson, 1995). This is especially true for pediatric recipients because there are fewer available longitudinal data about psychosocial risks for this population.

A review of existing studies concluded that "one of the most consistent findings across studies is that family and social support is predictive of positive psychosocial outcome (post-transplant)" (Engle, 2001). A recent report found that dysfunctional parent–child interactions are associated with nonadherence to medications in pediatric kidney transplant recipients (Gerson et al., 2004). Although this is not always the case, child abuse

may lead to a severe disruption of family support because the family ceases to be supportive and becomes a threat. Nevertheless, a history of child abuse has never been specifically evaluated as a predictor of poor outcome in any transplant setting.

The present prospective study evaluated the relationship between a history of child abuse, adherence to an immunosuppressive regimen, and medical outcome in a cohort of pediatric liver transplant recipients. We also evaluated the existence of domestic violence (violence directed against a spouse, not a child) and the presence of both parents at home as potential predictors of poor outcome due to disruption of the family structure in nonabuse cases.

METHOD

Patients

We recruited children and adolescents who came to scheduled (nonurgent) clinic visits between January 1, 2002 and December 31, 2002 in a major pediatric liver transplantation center. To enroll, patients needed to be medically stable (defined as the clinic visit did not identify a current reason for admission and did not result in an immediate referral to the emergency department). The reason for this requirement is twofold. First, unstable patients and their families may be reluctant to spend time with an investigator trying to probe their past (that would affect their likelihood of being forthcoming with information related to abuse). Second, unstable patients may have fluctuating liver function tests and blood level values, and these are used as outcome measures in this study. If the cohort's outcomes were already poor at the outset, then it would have been difficult to tie any deterioration (in the entire cohort) to a factor that is being discovered during the abuse evaluation. Furthermore, if outcomes are already compromised, it is less important to identify risk factors at this stage (it is already known that the patient is at risk).

Patients were eligible for the study if they were 8 to 21 years of age at the time of assessment, received a liver transplant 6 months or more before the evaluation, and assented (child younger than 18 years of age) and consented (parent or a child who is 18 years of age or older) to study procedures. Only children who have been prescribed tacrolimus (an immunosuppressant) regimen and were expected to have at least two recorded blood levels of tacrolimus in 2003 were eligible. This is because our adherence outcome measure was dependent on the use of several blood levels of tacrolimus. The study involved a full informed consent/child assent and was approved by the institutional review board. The consent document specifically stated that if previously undisclosed abuse is revealed in the interviews, the investigators may need to report the case to the child protective services. This clause was inserted because in New York, clinicians are "mandated reporters" of abuse.

Procedures

Evaluations took place in 2002. Abuse history was obtained by direct questioning of the child and parent and by review of pre- and posttransplantation psychosocial assessment records (see below).

Definitions of Child Abuse and Domestic Violence

Child abuse was defined (New York State Office of Children and Family Services, 2007) as inflicting "serious physical injury" or causing "a substantial risk of serious physical injury" or committing "an act of sex abuse" against the child. Domestic violence was defined as "the physical or sexual abuse to an individual perpetrated by a current or former intimate partner" (Rodriguez et al., 1999). We did not include the harder-to-substantiate category of psychological abuse in our definitions. Thus, all cases of domestic violence included the experience (by a parent) of an actual act of physical or sexual violence.

Assessments

Abuse/Domestic Violence History. Mandated documentation of a psychosocial evaluation pretransplantation, which includes documentation of abuse and domestic violence, was available for all of the patients. The investigative team (three female doctoral-level psychology interns) further directly asked each patient and parent, separately, about a history of abuse or domestic violence. Each parent was asked three questions: Did you ever have a forced sexual encounter? Did another person ever injure you on purpose? Did your child ever experience physical injury or sexual abuse from you or another person? A positive answer to any of these questions led to clarifying questions and appropriate coding. Any positive answer generated exploratory questions (e.g., if a parent disclosed having been raped, we proceeded by asking questions both about that incident and also about the child's experiences). Every child was similarly asked about "having been inappropriately touched" and/or "having experienced a forced sexual encounter" (phrasing depended on age), "another person injuring the child on purpose or a real risk that this may happen," and about "knowing about any act of violence against your mother or father." Further exploration was attempted for all positive answers. If needed, follow-up sessions were scheduled. Discrepancies in reporting, if present, were presented to the child and/or parent who was asked to explain these discrepancies. The final determination was made by a social worker who reviewed the pretransplantation evaluations and interview results, but was not aware of the medical outcome data and did not directly question the patients in the prospective evaluation protocol. We confirmed that abuse histories were reported to the State Child Protection Agency (any state within the United States) by reviewing the psychosocial pretransplantation records. A notation about reporting to the state, along with the specific mention of a state employee who was contacted or assigned to the case, was considered as positive proof of state-reported abuse.

Presence of Both Parents at Home

History of parental separation (biological parents of the child are not living together, and the child has only one parent at home) was verified by direct questioning of the parent.

Medication Adherence

As part of routine medical care, tacrolimus trough blood levels are obtained at every visit for each patient. Tacrolimus levels were examined at the Mount Sinai Medical Center laboratory. The levels were determined by the use of a standard enzyme-linked immunosorbent assay on patient whole-blood samples (Alak, 1997). The number of tacrolimus assays varies for each patient

because clinicians may elect to perform more or less frequent monitoring of levels based on patient characteristics and target medication blood levels. The use of SDs of consecutive blood levels of tacrolimus in pediatric liver transplant recipients, obtained over a period of 1 year, has been evaluated as a measure of adherence (Shemesh et al., 2004). A higher SD means more erratic levels and poorer adherence (Shemesh et al., 2004). This measure of adherence predicts adherence-related outcomes in children who had a liver transplant (Bucuvalas et al., 2005; Kerkar et al., 2006; Shemesh et al., 2000, 2004). We used SD of tacrolimus levels obtained during 2003 for each patient as the adherence measure.

Medical Outcomes

Alanine aminotransferase (ALT) levels are measured at each visit for every pediatric liver transplant recipient. The number of ALT assays obtained per each patient varies based on the clinician's determination and findings. As a measure of fluctuations in medical status, we used the SD of ALT levels collected during 2003. We also used the maximal ALT level during follow-up as a measure of outcome in each patient during 2003. These are two distinct measures. We further recorded all biopsy-proven rejection episodes during 2003 (an adherence-related measure of outcome [Molmenti et al., 1999]).

Comparison Groups

The following are the main comparisons in our study:

1. Children who were abused versus all other children.
2. Nonabused children who were exposed to domestic violence versus nonabused children who were not exposed to domestic violence. This comparison was chosen to assess the influence of disrupted families (as opposed to actual child abuse) on outcome in our cohort.
3. Nonabused children who had versus those who did not have two parents at home. This comparison was also chosen to assess whether the presence of only one adult in and of itself (as opposed to child abuse by one parent) had an effect on outcomes in our cohort.

Statistical Analyses

Analyses were performed using the SPSS 12.0 statistical package. All of the medical outcome relationships that we analyzed were predefined before the protocol began (i.e., "abused cases will have more biopsy-proven rejection episodes"). Independent-sample t tests were used to compare means of continuous variables (SD of ALT levels, maximal ALT values, and tacrolimus SD) between the groups described in the above comparisons. To investigate the relationship between adherence to medications and medical outcome, Pearson correlations were computed between the SD levels of tacrolimus, SD of ALT, and maximal ALT. We performed simple comparisons between predefined groups (i.e., Fisher exact tests) because of small sample sizes. A Fisher exact test was used to examine the relationship between a history of abuse (yes/no) and the presence of biopsy-proven rejection episodes. Chi-square tests were used to evaluate the significance of differences between predefined group characteristics (i.e., race) as described in the text. Statistical tests were two-tailed whenever applicable.

A p value (α level) of $\leq.05$ was chosen as the level of statistical significance. Because in the main hypothesis there were three medical outcome variables that were evaluated as a function of the abuse history (maximal ALT, fluctuation in ALT, biopsy-proven rejection), we applied the Bonferroni correction to account for multiple tests of significance in the medical outcome comparisons. Thus, for tests of significance using medical outcome measures, the adjusted p level was determined to be .05/3 = .017.

RESULTS

Figure 1 presents recruitment and patient flow data. Seventy-two patients who potentially met inclusion criteria came to the clinic in 2002. All were approached by our team. Of those, 58 patients consented. Reasons given by the remaining patients for declining participation were primarily related to lack of time for the required interview. Of the 58 patients enrolled in the study, two received cyclosporine rather than tacrolimus. Therefore, the SD method to evaluate blood levels was not applicable in their case. These patients were excluded, for a final cohort of 56. As determined by our protocol, the investigative team did not intervene with medical care provided during 2003. All of the patients were seen at least once, but three patients had only one tacrolimus level and one ALT level recorded during 2003; these patients were excluded from the SD calculations for tacrolimus and ALT. Patients who were included in the SD analyses had 3 to 44 tacrolimus assessment points (mean 14.64, median 12, SD 9.60) and 3 to 45 ALT assessment points (mean 16.19, median 14, SD 10.42).

Baseline Characteristics

Patient baseline characteristics by groups are presented in Table 1. Patients had 14 different illnesses that led to a liver transplantation. Biliary atresia was the most common diagnosis (23 patients, 41%).

Abuse and Violence Exposure

Five patients (9%) had a state-documented history of child abuse, and all of them disclosed this history when interviewed (no discrepancies were found between interview results and chart notes). The interviews did not identify any cases that were not already reported. There was no significant age difference between patients who were abused or not (age, N = 56; t = 0.888; p = .38; 95% confidence interval [CI] -4.44 to 1.72). There was no significant difference between ethnic groups studied and abuse history (ethnicity, χ^2 = 0.635, p = .64). Four abused children were females. None of the cases were under active state investigation
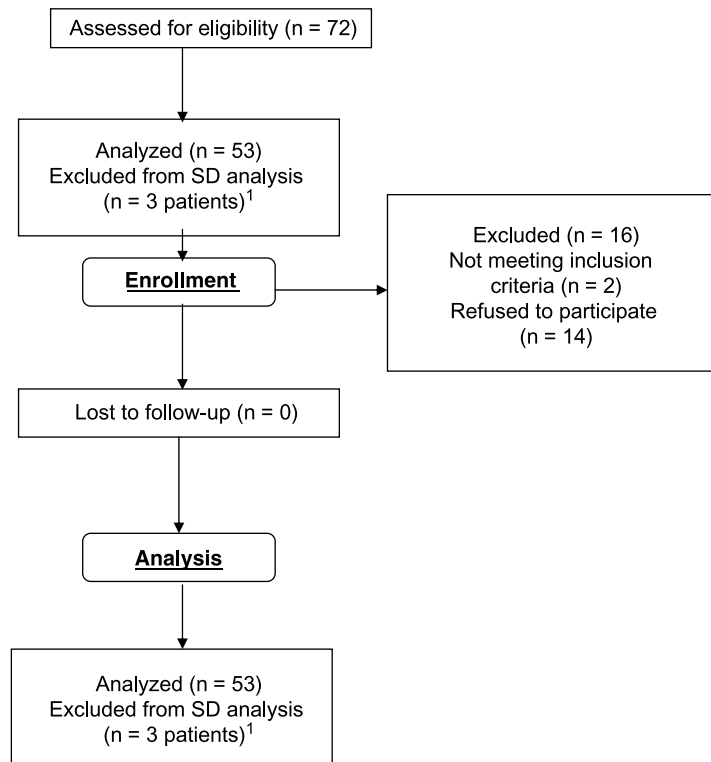
Fig. 1 Patient enrollment flowchart. [1]Three patients had only one reading of tacrolimus and ALT (alanine aminotransferase); these were excluded only from SD analyses for both tacrolimus and ALT. This is because it is impossible to compute an SD for one reading only.

in 2003 (current abuse was not suspected in any of the cases). The characteristics of each case of child abuse are presented in Table 2.

Eleven patients (20%) were identified as having been exposed to domestic violence in the past. Similarly to the abuse cases, no current cases were identified. There was no significant age difference between patients exposed or not exposed to domestic violence (age, $N = 56$; $t = 1.45$; $p = .23$; 95% CI -0.61 to 3.76). Hispanic children were significantly more likely to be exposed to domestic violence than other children (ethnicity, $\chi^2 =$ 6.29; $p = .043$). Among the nonabused patients, 29 patients had only one parent at home when the evaluation took place. A χ^2 test showed that there was no relationship between exposure to domestic violence and whether the child had one or two parents at home ($p = .27$).

Medical Outcomes, Abuse, Domestic Violence, and Parents' Presence at Home

The tables depict differences in three of the groups studied. Detailed descriptions of the findings and their statistical significance are presented below.

TABLE 1
Baseline Characteristics

Cohort	No. of Patients	Age, y (mean ± SD)	Age range, y	Sex (M/F)	Race % (W/H/B)
Abuse history	5	16.6 ± 3.0	13–21	1/4	1/2/2
Domestic violence	11	14.1 ± 3.0	11–21	5/6	0/8/3
One parent at home, no abuse	29	14.7 ± 3.5	9–21	16/13	5/16/8
Two parents at home, no abuse	22	15.9 ± 3.0	10–20	9/13	11/8/3
No abuse/no domestic violence	40	15.6 ± 3.3	9–20	19/21	16/16/8

Note: M = male; F = female; W = white; H = Hispanic; B = black.

TABLE 2
Historical and Medical Details for Abused Patients

No.	Type of Abuse	Age at Time of Abuse	Age at Transplantation	Age	Lives With Perpetrator	Dx	ALT SD	Max ALT	SD of Tacrolimus (Adherence Measure)	Rejection
1	Physical	6	8	21	No	EHBA	25.52	128.00	4.18	No
2	Physical	8	2	13	No	EHBA	21.50	179.00	3.21	No
3	Severe physical threat	6	10, 13 (2 transplants)	16	No	AIH	184.00	845.00	5.15	Yes
4	Severe physical threat	12	5	15	Yes	AIH	197.40	693.00	3.22	Yes
5	Physical	5	12	18	No	AIH	234.96	857.00	2.94	No

Note: Dx = diagnosis; ALT = alanine aminotransferase; EHBA = extrahepatic biliary atresia; AIH = autoimmune hepatitis.

- Medication adherence (Table 3): In each comparison, patients with a history of abuse were significantly less adherent than the other patients. There were no significant differences between children who had and had not been exposed to domestic violence and between patients who had versus did not have two parents at home.
- Medical outcome and abuse/domestic violence/parents' presence at home (Tables 4 and 5): In each comparison, patients with a history of abuse had significantly ($p < .017$) worse outcomes than other patients, but there were no significant differences between children who had versus had not been exposed to domestic violence and between patients who had versus did not have two parents at home.
- Rejection episodes: Two patients in this cohort experienced a biopsy-proven rejection episode during 2003. Both of these children had a history of abuse. Hence, patients with an abuse history were significantly more likely to have a rejection episode than those with no history of abuse ($p = .006$, Fisher exact test).

Medical Outcomes and Adherence

Higher tacrolimus SD (erratic adherence) was significantly associated with higher ALT SD (erratic disease control; $r = 0.34$; $p = .02$). Similarly, higher tacrolimus SD was also significantly associated with higher maximal ALT (indicating disease progression; $r = 0.32$; $p = .02$).

DISCUSSION

Liver transplant recipients with a history of abuse documented by the state had significantly poorer medical outcome during the year of follow-up. Of special note is that the two cases of biopsy-proven rejection episodes in this cohort both occurred in abused children who were nonadherent to tacrolimus. Therefore, it seems that psychosocial predictors rank highly among all potential predictors for acute graft rejection in otherwise stable outpatient pediatric liver transplant recipients. A history of abuse emerges as a significant correlate with poor outcome. A meta-analysis examining studies of women who were sexually abused (Neumann et al., 1996) noted that various effects of abuse have been identified; these can "get lost" if not specifically assessed. Therefore, obtaining a history of abuse should become a routine part of pre- and posttransplantation evaluations. A positive history should trigger a more thorough evaluation of potential consequences and risks.

TABLE 3
SD of Tacrolimus Levels in Different Groups (Higher SD = Less Adherence)

	Mean Group 1	Mean Group 2	*t*	*p*	CI
Abuse vs. no abuse	**3.74**	**2.29**	**–2.40**	**.02**	**–2.66 to –0.24**
DV vs. no DV	2.50	2.23	–0.61	.54	–1.19 to 0.63
Both parents at home vs. only 1 at home	2.26	2.32	–0.15	.88	–0.83 to 0.71
Abuse vs. DV	**3.74**	**2.50**	**–1.78**	**.01**	**–2.72 to –0.25**
Abuse vs. only 1 parent at home	**3.74**	**2.32**	**–2.55**	**.02**	**–2.56 to –0.28**

Note: Significant differences between groups are shown in bold. DV = domestic violence.

TABLE 4
ALT SD in Different Groups (Higher ALT SD = Less Stable Medical Outcome)

	Mean Group 1	Mean Group 2	*t*	*p*	CI
Abuse vs. no abuse	**132.67**	**24.12**	**−5.11**	**.00**	**−151.19 to −65.91**
DV vs. no DV	18.23	25.87	0.60	.55	−17.85 to 33.13
Both parents at home vs. only 1 at home	23.50	24.65	−0.11	.92	−22.74 to 20.44
Abuse vs. DV	**132.67**	**18.23**	**−3.46**	**.00**	**−185.36 to −43.52**
Abuse vs. only 1 parent at home	**132.67**	**24.65**	**−4.42**	**.00**	**−156.95 to −59.10**

Note: Significant differences between groups are shown in bold. Significance level determined to be $p \leq .017$ (see text). ALT = alanine aminotransferase; DV = domestic violence.

This study used the SD of tacrolimus blood levels as the adherence measure. Tacrolimus is a calcineurin-inhibiting immunosuppressant that is routinely used in transplantation centers and is prescribed so as to achieve a "target" blood level in each patient (Rhee and Bousvaros, 2004). Routine measurement of tacrolimus blood levels is the standard of care in pediatric liver transplantation centers, and thus it is possible to use clinically obtained data to measure adherence in this setting (Shemesh, 2004a). Addressing fluctuations in calcineurin inhibitor blood levels has been described as a way to improve posttransplantation care (Bucuvalas et al., 2005).

There are many possible methods to measure adherence in patients with gastrointestinal illnesses (Shemesh, 2004b). The tacrolimus SD method has the advantage of being a direct measure of adherence: it is objective and is taken over time (i.e., it incorporates data from multiple measures). This method takes advantage of the fact that there is a linear relationship between tacrolimus intake and its blood levels in patients who receive a liver transplant (Cakaloglu et al., 1994). Tacrolimus absorption is independent of the presence of bile acids and is less affected by entero-pathies than other immunosuppressant medications (Rhee and Bousvaros, 2004). Hence, although theo-retically an altered metabolism in the same patient can also alter blood levels of this medication, in practice this rarely happens.

The degree of fluctuation in tacrolimus blood levels was shown to predict adherence-related outcome (Kerkar et al., 2006; Shemesh et al., 2000, 2004). It is correlated with electronic monitoring of adherence, which uses medication bottles with a computer chip on their caps that records each opening of the bottle (Kerkar et al., 2006). It is also correlated with a panel assessment of adherence (Shemesh et al., 2000) in children who had a liver transplant. Fluctuation in the levels of another calcineurin inhibitor, cyclosporine, was shown to be related to poor outcomes in heart transplant recipients (Flippin et al., 2000). Therefore, in the transplantation setting, medication-level fluctua-tion has been used as a measure of adherence, was shown to predict poor outcomes posttransplantation, and has been correlated with other measures of adherence.

Long-term sequelae of child abuse are well docu-mented (Briere and Runtz, 1993), yet the present article is one of only a few that prospectively examined the relationships between a history of child abuse, medica-tion adherence, and poor medical outcome in patients with a life-threatening medical condition (Abdale,

TABLE 5
Maximal ALT in Different Groups (Higher Maximal ALT = Less Stable Medical Outcome)

	Mean Group 1	Mean Group 2	*t*	*p*	CI
Abuse vs. no abuse	**540.40**	**108.76**	**−4.75**	**.00**	**−613.72 to −249.55**
DV vs. no DV	95.91	112.30	0.27	.79	−103.67 to 136.45
Both parents at home vs. only 1 at home	106.50	110.48	−0.08	.94	−103.76 to 95.79
Abuse vs. DV	**540.40**	**95.91**	**−3.37**	**.01**	**−727.75 to −161.23**
Abuse vs. only 1 parent at home	**540.40**	**110.48**	**−4.42**	**.00**	**−628.02 to −231.82**

Note: Significant differences between groups are shown in bold. Significance level determined to be $p \leq .017$ (see text). ALT = alanine aminotransferase; DV = domestic violence.

1999; Arriola et al., 2005; Berkowitz, 1998; Lurie et al., 2000). A link between nonadherence to medical recommendations and abuse was previously documented in patients with human immunodeficiency virus infection (i.e., Abdale, 1999). Other findings have suggested that abuse is associated with nonadherence and death after liver transplantation (Lurie et al., 2000) and that dysfunctional parent–child relationships are associated with nonadherence posttransplantation (Gerson et al., 2004). This association between abuse and nonadherence, we believe, merits much more intensive research because it can point the way to focused interventions; it may be possible to focus on improving adherence in medically ill abused children as a way to improve their outcome.

There are several other mechanisms that could explain why abuse may be related to nonadherence to medical recommendations and poor outcome in these patients. First, in cases in which abuse precedes the transplantation, a history of traumatic exposure such as abuse may lead to a higher likelihood of perceiving the medical procedure (transplantation) itself as traumatic. Patients who were abused may be more likely to be traumatized further by the medical event (transplantation in this case) and hence avoid taking medications. Second, some of the cases of abuse in the present study occurred after transplantation; indeed, medical disability has been associated with increased incidence of abuse (Tonmyr et al., 2005). In cases in which abuse occurs after the transplantation, children may come to associate the transplantation with the event that "caused" the abuse situation and "blame" the physicians as responsible (and thus not follow the physician's recommendations). Third, abused children may distrust adults and authority figures (Briere and Runtz, 1993) and therefore be less likely to follow their physician's recommendations. Fourth, engaging in risk-taking behaviors, which is associated with abuse (Dube et al., 2001; Lodico and DiClemente, 1997), may lead to poor outcome in transplant recipients. Fifth, the biological alterations that have been noted in abuse survivors (Altemus et al., 2003; Nemeroff, 2004) may predispose transplant recipients to graft rejection or increased likelihood of medical adverse events.

Our study did not address the potential mechanisms that may link a history of abuse with poor medical outcomes and nonadherence, and further research is needed to identify these mechanisms. One potential explanation for our finding is that abuse in and of itself may not have been the cause of the poor outcome. Abuse may simply be an indication that other risk factors (i.e., dysfunctional families, inability to provide a cohesive structure that would foster adherence) are present in the identified families; however, because there was no association between domestic violence and poor outcomes, our study provides some evidence that disruption of family structure may not be the only culprit. Our finding that adherence did not seem to be worse in single-parent versus two-parent families should be interpreted cautiously. More descriptions of family life and history, possibly using standardized questionnaires, would have been appropriate if we were to investigate family cohesiveness in a reliable manner. We report the results of comparisons between families with one versus two parents at home, therefore, not as a proxy measure for family cohesiveness but simply as a way to compare whether the lack of availability of a second adult at home could, in and of itself (but without the added complication of abuse), account for lack of adherence to medical recommendations. If this was so, then it would have been presumably because of less supervision and would have suggested that the important mechanism by which abuse exerts its influence is mediated through the simple lack of a supervising adult. It is not surprising, in this context, that we did not find an effect; children can be supervised well by one parent, and conversely the presence of two parents does not necessarily guarantee good supervision. This finding highlights the need for a specific measure or assessment of parental supervision on the way to reach valid conclusions about adherence. Our results suggest that it is incorrect to assume that the presence of two parents is superior (in terms of supervision and adherence) to the presence of only one adult at home. The important factor seems to be not the number of adults, but the way they specifically deal with the child.

Domestic violence seemed to be more prevalent in Hispanic patients in this cohort; however, this was not one of our a priori hypotheses and we cannot verify, because of the small sample size, that this finding is generalizable. Further research may be indicated to verify whether indeed domestic violence is more prevalent in Hispanic populations in this setting. The finding that abuse alone (but not domestic violence exposure) was associated with poor outcome would

appear to contradict previous studies that linked domestic violence to poor psychosocial outcomes in children (e.g., Wolfe et al., 2003). One potential explanation for this discrepancy could be that the association between poor outcome and domestic violence is weaker than the association between abuse and poor outcome. Our relatively small sample size allowed the identification of only robust relationships in this cohort. Larger studies are needed to identify less dramatic risk factors.

A word of caution is warranted: our results should not be interpreted as supporting the idea that a history of abuse should be viewed as a reason to avoid performing transplantations in the victims (children). There are ways to address both the consequences of abuse (e.g., Cohen et al., 2004) and the risk factors associated with it. Hence, before abuse is considered a factor in placement on transplant lists, research is needed to investigate whether available treatments are adequate in restoring adherence and improving outcomes (if they are, then the right way to go is to treat these patients adequately rather than reduce their chances of receiving a transplant).

Limitations

The study was conducted in only one institution. Patients were recruited only when medically stable (6 months posttransplantation, appointments at scheduled clinic visits rather than urgent visits) to conduct the interviews in as relaxed a context as possible, but this undoubtedly limited the number of patients whom we could address in this protocol. Because abuse information was corroborated with recorded state reports, a positive history of abuse in this study was not subject to error in recall, but negative histories may have been subject to recall bias (parents or children may have consistently but erroneously reported negative histories). Our evaluation may have missed some cases that were not disclosed by participants who may have been concerned about the potential consequences of mandated reporting. The fact that all of the cases that were "discovered" by the research team have already been reported to the state suggests that only parents who knew that the abuse was well documented were willing to disclose it. There may have been other undisclosed cases that we missed. However, the fact that we did find clear associations with poor outcomes in cases of

well-documented and openly acknowledged abuse suggests that it is possible to identify at least some of the vulnerable cases through a straightforward evaluation.

Although the adherence measure that we used (SD of tacrolimus levels) is the best studied measure of adherence monitoring in this patient population, limitations remain (Shemesh, 2004b). The most important limitation is that this measure may not detect "white coat" nonadherence; that is, patients who consistently only take the medication before a laboratory test. Although this is theoretically possible, it is likely that in the pediatric transplant setting the medical outcomes of such patients would deteriorate rapidly and they would not be able to persist in not taking the medications for a full year of follow-up (they will eventually suffer from a rejection and may even die). Another potential limitation is that fluctuation in medication blood levels can result from variability in physician prescription patterns, rather than be an indicator of patient nonadherence. This limitation would be expected to come into full effect in multicenter studies of adherence and is less important in a single-center study (such as the present one), in which patients were treated by the same physicians over time.

Abuse history may be a sensitive topic to discuss. The fact that we conducted face-to-face interviews over a specified period of time that was determined by the design of the protocol (during 2002 but not later) may have led to diminished reporting if patients did not have the time to establish rapport with the interviewer. It is also possible that the interviewer may not have felt comfortable probing further in questionable cases. Nevertheless, it is of note that when different methods of assessment of child abuse have been compared (paper-and-pencil measures, interview, or a computer-delivered questionnaire) in a large sample of interviewed adults, the rates of abuse disclosure were the same for interviews as with other measures (DiLillo et al., 2006). This suggests that in spite of the theoretical limitations of the interview as a tool to discover abuse, it is probably as good as the other available possibilities (these, in turn, also have their own specific limitations).

A limitation introduced by the small numbers is that we may have missed relatively weak associations. Because of the small sample size, our findings should certainly be read as suggestive rather than conclusive;

however, the limited number of pediatric liver transplant recipients in any institution would make it difficult to reach higher numbers unless a multicenter extensive study was conducted. Until such time, our results could be used— tentatively if not conclusively— by transplantation centers that wish to create an evidence-based psychosocial assessment packet.

Clinical Implications

A history of abuse should be routinely evaluated in transplantation-related psychosocial evaluations. The fact that patients and families were forthcoming about this history suggests that the abuse history evaluation is feasible in clinical settings. The fact that abuse is associated with poor outcomes posttransplantation (whether it is the actual direct cause for the poor outcome) means that identifying cases with a history of abuse would lead to the identification of at-risk patients who can then be monitored more closely. These patients should also receive an in-depth psychosocial evaluation and follow-up both before and after transplantation. The finding that nonadherence is associated with abuse suggests that medication blood levels of patients with a known history of child abuse should be followed gingerly in the transplantation setting.

Cognitive-behavioral therapy has been shown to be efficacious for posttraumatic stress disorder in children who have been abused (Cohen et al., 2004, 2005), and it may be indicated in some of the cases that we have evaluated. Further research to understand the reasons for the association between abuse and poor outcomes in youths receiving transplants is warranted before any specific intervention modality can be recommended.

CONCLUSIONS

A history of child abuse emerges as an important risk factor that should be assessed in transplant recipients. Special attention should be given to adherence to medical recommendations in pediatric transplant recipients who have a history of child abuse. Further research is needed to define the mediating variables in the relationship between abuse, nonadherence, and poor outcome posttransplantation and to evaluate specific treatment strategies in these vulnerable patients.

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