

A Pilot Study of Posttraumatic Stress and Nonadherence in Pediatric Liver Transplant Recipients

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ABSTRACT. *Background.* Symptoms of posttraumatic stress disorder (PTSD) were described in survivors of life-threatening diseases, the trauma being the experiences associated with the disease or its treatment. Their prevalence in liver transplant recipients is unknown. Based on clinical observations, we hypothesize that a significant proportion of pediatric liver transplant recipients suffers from PTSD symptoms. We further hypothesize that nonadherence (noncompliance) to medical management may, in some cases, be associated with these symptoms. Traumatized patients, according to this hypothesis, will avoid taking their medications, because these serve as painful reminders of the disease.

Objectives. To determine the prevalence of PTSD symptoms in a sample of pediatric liver transplant recipients. To determine whether symptoms of PTSD are associated with nonadherence in these patients. To describe the clinical presentation of PTSD and the management of severe nonadherence in patients who suffer from this disorder.

Methods. Nineteen pediatric liver transplant recipients and their caretakers were interviewed, using the UCLA Post Traumatic Stress Disorder Reaction Index (PTSRI). Data were obtained on a few demographic parameters and perception of disease threat. Adherence was evaluated by 2 methods: 1) a clinician panel (taking into account the clinical sequelae of severe nonadherence); and 2) computation of the standard deviations (SDs) of consecutive determinations of blood levels of Tacrolimus (a higher SD means higher variability between individual measures and is therefore an indicator of nonadherence). As an illustration of the general phenomenon, we describe 3 cases of liver transplant recipients who were nonadherent and who suffered from PTSD.

Results. Six of 19 patients had positive scores on all 3 components of the PTSRI (PTSD patients). Three of these, and none of the others, were considered significantly nonadherent by the panel. Therefore, nonadherence was significantly associated with the existence of symptoms from all 3 domains of PTSD (Fisher's exact test) in our sample. In particular, a high avoidance score on the PTSRI was highly correlated with panel-determined nonadherence. Further, SD of medication levels were significantly higher in PTSD patients, compared

with the rest of our sample. No significant differences were found in perception of disease threat or demographic variables between PTSD patients and the rest of our sample. The 3 cases that we describe became adherent to their medications when symptoms of PTSD subsided during the course of therapy.

Conclusions. Clinically significant nonadherence, determined by 2 different methods, was associated with the full spectrum of PTSD symptoms in this sample. It was especially associated with a high avoidance score, which suggests that avoidance of reminders of the disease (eg, medications) may be a mechanism of nonadherence. Screening for and management of these symptoms, therefore, may improve adherence. This novel concept may be applicable to other patient populations. However, more data are needed before any definite conclusions can be drawn. *Pediatrics* 2000; 105(2). URL: <http://www.pediatrics.org/cgi/content/full/105/2/e29>; *posttraumatic stress disorder, liver transplant, nonadherence.*

ABBREVIATIONS. PTSD, posttraumatic stress disorder; PTSRI, Posttraumatic Stress Disorder Reaction Index; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ALTTIQ, Assessment of Life Threat and Treatment Intensity Questionnaire; SD, standard deviation.

Nonadherence to medical management remains a major cause of morbidity and mortality in various settings.¹ It is considered a significant contributing factor to organ loss among patients who survive kidney, heart, and liver transplants.² A recent study reported 34 episodes of nonadherence among 28 pediatric liver transplant recipients, associated with acute cellular rejection and recurrent hepatitis in 16 patients, death in 2 patients, and loss of 5 transplants, demonstrating that nonadherence in this population is common and dangerous.³ Unfortunately, the causes of nonadherence in pediatric patients remain largely elusive.⁴ At present, effective treatment techniques are not always beneficial or applicable.⁵

We present a novel hypothesis that conceptualizes nonadherence, in some cases, as linked to symptoms of posttraumatic stress disorder (PTSD), which is a psychiatric disorder originally linked to combat experience. PTSD is a dysfunctional response to severe stress that is characterized by 3 clusters of symptoms.⁶ Patients typically report flashbacks of traumatic events ("Reexperiencing" dimension), avoidance of reminders of the stressor ("Avoidance" dimension), and prominent anxiety and hypervigilance.

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lance (“Hyperarousal” dimension). Although initially thought to be exclusively linked to war and natural disasters, it has recently been recognized that a variety of stressors can lead to PTSD, including life-threatening diseases.⁷ Symptoms of PTSD were shown to be present in subsets of pediatric cancer survivors⁸ and in a group of pediatric bone marrow transplant recipients.⁹ There are no published data regarding the occurrence of PTSD in liver transplant recipients.

Liver transplantation involves a major surgical procedure, several days of intensive care, and a disfiguring abdominal scar. It is usually performed on patients who suffer from a chronic, life-threatening, and debilitating disease before the transplant. Any of the above factors may be traumatic. The essential aspect of a precipitating event for PTSD, according to the current diagnostic criteria, is that it leads to a response of intense fear, helplessness, or horror.⁶ Although a liver transplant is planned and life saving, the illness and the operation can still constitute a traumatic event because such a response may be generated in the child and the parents. Therefore, we hypothesized that some pediatric liver transplant recipients suffer from symptoms of PTSD. We further hypothesized that these patients may become non-adherent as a part of the Avoidance dimension of their symptoms. For example, a child will not take the prescribed immunosuppressant medication because taking it serves as a recurrent reminder of the painful experience. We assume that existence of all 3 symptom clusters—not just avoidance symptoms—is needed to produce significant nonadherence. This conceptualization of nonadherence was not previously described, and it may have therapeutic implications. Current treatments of nonadherence do not focus on the trauma associated with the medical disease itself.⁴ Addressing this factor in treatment may prove beneficial. We report a survey of the existence of PTSD in this population and its relationship with nonadherence. Following this survey, we have treated several transplant recipients who were nonadherent and who suffered from transplant-related PTSD in our institution. We present 3 case reports detailing the clinical presentation and management of these patients, illustrating the clinical importance of this phenomenon.

PATIENTS AND METHODS

Patients

We compiled a list of all liver transplant recipients who were currently 8 to 20 years of age and had a transplant at least 1 year before the study period. Thirty patients met age criteria and had a transplant between 1988 and 1997 in our institution. Eight were not available to the interviewers because of relocation. The remaining 22 patients constitute our sample. These were not the same patients that we describe in the case reports.

Consent and Assent

The study was approved by our institutional review board and involved formal consent procedures for parents and children who were 17 years of age and older. Assent was obtained from all participants who were younger.

Interviews

Patients and their primary caretakers (when available) were interviewed by the investigators (E.S., S.L., and Y.P.). We used the UCLA Posttraumatic Stress Disorder Reaction Index (PTSRI).¹⁰ This index was previously used in a large sample of pediatric cancer patients⁸ and is rated in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria.⁶ An earlier version of this measure has been found to have a high correlation with a clinically derived diagnosis of PTSD.¹¹ It has 3 different domains, corresponding to the Reexperiencing, Avoidance, and Hyperarousal dimensions of PTSD. Index criteria mirror the DSM-IV formulation so that the number of symptoms that need to be present for each category to be positive is the same. The designation “full PTSD likely” is given only if all 3 domains are positive in the context of a traumatic event. If 2 of 3 domains are positive, the designation is “partial PTSD.” The parental questionnaire asks the parent to assess the child’s symptoms and rate them. Therefore, the parent version of the PTSRI is designed for a parental rating of the child’s PTSD symptoms; it is not an assessment of the symptoms that the parents themselves may have. A modified version of the Assessment of Life Threat and Treatment Intensity Questionnaire (ALTTIQ)⁸ was also administered to assess the perceptions of both the patient and the caretaker of the severity of the disease. A lower score on this instrument means that the patient perceives his illness as more threatening or severe. Finally, data on the socioeconomic background of the patients, including family size, number of parents living with the patient, apartment size, address, and ethnic background were collected. The interviewers were blind to the adherence status.

Measurement of Adherence

There is significant controversy regarding the definition and measurement of nonadherence, and no gold standard is available.¹² It is possible that some degree of nonadherence is acceptable.⁴ We did not attempt a comprehensive evaluation of nonadherence in our study population. Rather, we attempted to elucidate whether patients who suffer from PTSD are likely to be clinically nonadherent (ie, nonadherent to the point that their health is in danger). We were interested in measures of nonadherent behavior over time, evaluated retrospectively. PTSD symptoms are likely to have existed since the transplant or shortly after it. Therefore, only a persistent pattern of nonadherence since the transplant should be assessed for the purpose of demonstrating a meaningful association. We have used 2 different methods to determine nonadherence in our sample. First, we convened a clinician panel that consisted of 2 hepatologists (P.V. and B.L.S.) and a clinic nurse (M.A.). The panel determined which patients were most severely clinically nonadherent, ie, nonadherent to the point that their health was in danger, and who displayed a recurrent, persistent pattern of nonadherence with their clinic visits, diet requirements, and medication intake. We specifically discouraged panel members from providing an opinion regarding recent nonadherence, it is the most problematic cases—the chronic, persistently nonadherent patients—that we were interested in detecting. The panel members were blind to the results of the structured interviews and to the adherence determinations of other panel members. Clinicians are likely to underdiagnose nonadherence,¹² and their decisions are influenced by health status (ie, they are more likely to diagnose nonadherent patients who are sick). The tendency to underdiagnose and the bias toward the diagnosis of medically sick patients serve our purpose, because we are interested in the association between PTSD and severe, clinically significant nonadherence, and not in nonadherence as a detached phenomenon. The issue of low agreement rate between clinicians was addressed by blinding each panel member to the decisions of other members and assessing the agreement between their determinations as a part of our results. Based on pilot assessments in a different population with the same panel, we expected a high level of agreement between members at the very severe spectrum of clinically significant nonadherence. Second, we calculated the standard deviation (SD) for series of blood levels of Tacrolimus for each patient, obtained regularly at the same time period over a year (or more) of follow-up. We were not interested in just 1 measure, because specific and time-limited nonadherence (exemplified, perhaps, by 1 single low blood level of a medication at the time of the interview) may not carry a clinical significance and may not accurately represent the long-term picture and course of

a specific patient. A measure of ongoing fluctuation of intake is preferable for our purposes. Tacrolimus blood levels were shown to be well correlated with dosage and intake in liver transplant recipients.¹³ This is not the case for cyclosporine levels.¹³ Therefore, patients receiving cyclosporine were excluded. In a review of different methods for the detection of nonadherence in transplant recipients,¹² others cautioned that medication levels may vary between 1 patient and the other based on different metabolic rates, the dynamic nature of nonadherence, and white coat compliance (eg, the patient who is taking the medication only before clinic visits). Examining fluctuation of blood levels rather than the levels themselves eliminates many potential factors (eg, patient-specific metabolic rate and elimination dynamics) that may confound the assessment and vary between patients. It could be argued that a persistently low intake (or no intake) would generate a low SD (no fluctuation, the patient is consistently nonadherent), and therefore, would be misread as adherence by this measure. However, nonadherence was previously described as dynamic in nature,¹⁴ that is, it is rarely the case that a patient is consistently not taking a particular proportion of a medication (eg, 20% at a time). In the case of patients who are not taking their medications at all, a blood level of zero would have been picked up by our clinicians and addressed immediately. Finally, this method would not detect the hypothetical group of patients who take their medications only before a clinic visit. We were not particularly interested in this group—a patient who consistently tries to elude detection will succeed, regardless of the method used. We were rather more interested in the detection of patients who become nonadherent because of stress, where an intervention might be beneficial. A higher SD, and therefore, increased variability between individual levels overtime, is a fairly specific but not a sensitive measure of nonadherence in our population, as intended.

Case Studies

We describe 3 pediatric liver transplant recipients who were nonadherent to medical recommendations and whose nonadherence resolved after an intervention addressing symptoms of post-traumatic stress. No accepted treatment is currently available for medical disease-related PTSD. However, our intervention strategy was informed by cognitive-behavioral approaches that are used in the treatment of victims of other forms of trauma.¹⁵ Patients described in the case reports were not enrolled in the survey.

Statistical Analysis

SDs of Tacrolimus levels for each individual patient were computed (n for each series >10). Therefore, we had, at the end of the analysis, a number (the SD) corresponding to the amount of fluctuation of blood levels for each individual patient. Groups were compared using a Student's t test. Fisher's exact test was used to determine the statistical significance of the association between the panel clinical determination of nonadherence and PTSD.

RESULTS

A Survey of Symptoms of PTSD and Nonadherence in Transplant Recipients

Of 22 potential patients, 19 were interviewed (Table 1). One patient did not consent to the interview, 1 could not understand the PTSRI, and 1 was not available during the study period. Fifteen primary caretakers completed the parental questionnaires (the rest were not available during the visit either because the patient was accompanied by another caretaker or, for older patients, because the patient was not accompanied by a caretaker at all). Two patients declined to answer the ALTTIQ, which was administered last. SDs were calculated for 15 patients who were receiving Tacrolimus. Four other patients receiving cyclosporine, our second-line immunosuppressant, were excluded from the statistical analysis of medication levels because cyclosporine assays are not readily comparable to Tacrolimus.

Of 19 patients, 6 had a high (positive) score on all 3 components of the patient-rated PTSRI—"full PTSD likely" by questionnaire criteria. Parents tended to underestimate their children's symptoms. The most striking difference was found in the Reexperiencing dimension (parental scores were lower than children's in 10 of 15 cases).

TABLE 1. Symptoms of PTSD and Nonadherence

Pt Number	Pt Reexp	Pt Avoid	Pt Arous	Pt Total	Par Total	Par Reexp	Dx	Adh Panel	SD	ALT TIQ	Age	Disease
1	6	15	13	34			Full	N	8.5	11	19	FHF
2	5	19	10	34	16	3	Full	N	3.3	17	15	EHBA
3	9	25	10	44			Full	N	7.4	14	20	Hep B
4	5	8	9	22	17	3	Full	A	csa	19	20	Cry C
5	7	13	10	30	19	4	Full	A	6.0	17	11	Cry C
6	8	16	8	32	33	8	Full	A	csa	16	11	INH tox
7	6	4	8	18			Part	A	4.1	19	20	EHBA
8	8	5	6	19	17	3	Part	A	4.7	18	9	Hep C
9	11	7	11	29	14	7	Part	A	1.2	16	10	EHBA
10	6	7	6	19	19	3	Part	A	2.3	12	11	AIH
11	2	11	5	18	9	0	Part	A	1.3	U/A	9	EHBA
12	3	9	2	14	14	6	Part	A	4.8	21	13	EHBA
13	7	1	4	12	16	4	No	A	.95	21	12	Wilson
14	1	5	15	21	21	0	No	A	.94	14	11	FHF
15	0	0	0	0	0	0	No	A	4.0	16	15	PSC
16	2	0	2	4			No	A	csa	22	20	PSC
17	1	0	11	12	29	7	No	A	csa	21	10	Wilson
18	9	7	1	17	6	0	No	A	4.3	15	18	Hep C
19	1	4	3	8	11	1	No	A	3.9	U/A	11	EHBA

Pt reexp indicates PTSRI score on the patient-reported reexperiencing dimension; Pt avoid, PTSRI score on the patient-reported avoidance dimension; Pt arous, PTSRI score on the patient-reported arousal dimension; Pt total, total score on the patient-reported PTSRI; Par total, total score on the parent-reported PTSRI; Par reexp, PTSRI score on the parent-reported reexperiencing dimension; Dx, diagnosis according to patient-rated PTSRI criteria ("full PTSD"—all 3 dimensions are positive, "partial PTSD"—2 of 3 are positive, "no PTSD"—none are positive); Adh panel, adherence status as determined by a clinician panel; N, Nonadherent; A, Adherent; SD, SDs of Tacrolimus blood levels; csa, cyclosporine A (excluded from analysis); ALTTIQ, scores, patient-rated Assessment of Life Threat and Treatment Intensity Questionnaire; age, age at study period (in years); disease, pretransplant diagnosis; FHF, fulminant hepatic failure (of unknown etiology); EHBA, extra hepatic biliary atresia; Hep, hepatitis; cry C, cryptogenic cirrhosis; INH tox, isoniazid toxicity, AIH, autoimmune hepatitis, Wilson, Wilson's disease, PSC, primary sclerosing cholangitis; and U/A, information unavailable.

Of the 6 “full PTSD” patients, 3 were considered nonadherent by all members of the panel, who all pointed to the same patients (100% agreement) as the “most severe and life-threatening cases of nonadherence.” No other patients were determined to be severely nonadherent. Therefore, there was a significant association between “full PTSD” and nonadherence in our sample (Fisher’s exact test $P = .02$). The nonadherent patients had a significantly higher avoidance score compared with the rest of our sample (Student’s t test = 3.06; $P = .007$). There were 6 patients who had a high score on 2 of 3 components of the PTSRI. None of these, and none of the rest of the patients, were considered nonadherent by the panel. SDs for Tacrolimus levels were available for 4 “full PTSD” patients and 11 others. Cyclosporine levels and SDs were not incorporated attributable to the lack of correlation between levels and intake in this medication.¹³ The “full PTSD” patients had significantly higher medication SD values, compared with the rest of our patients (mean SD of 6.3 for the PTSD group, 2.95 for the rest; $t = 3.22$; $P = .007$). There was no significant difference between the group of patients who exhibited symptoms from only 2 of 3 domains and the rest of our sample. Similarly, there were no significant differences in perceived severity of illness, as assessed by the ALTTIQ, between the nonadherent and adherent patients and between the PTSD and non-PTSD groups. However, a nonsignificant trend toward lower scores (and, therefore, perception of the disease as more threatening) was found comparing the “full PTSD” group to the rest of the sample (mean scores: 15.6 and 17.7, respectively).

There was no significant difference between PTSD patients and the rest of the sample in apartment size (sample mean: 3.6 rooms per family; PTSD patients mean: 2.8; range: 2–6), or family size (sample mean: 4.5 per household; PTSD patients mean: 4.0; range: 2–10). Three of 6 “full PTSD” patients had only 1 parent at home, compared with 6 of the remaining 13 “non-PTSD” patients. The ethnic background of the PTSD patients (4 Hispanic, 1 white, and 1 Indian) and the rest of the sample (5 Hispanic, 3 blacks, and 5 whites) was representative of our general clinic population. PTSD patients were somewhat older than the rest (means: 16 and 13 years of age, respectively).

Case Reports

Case 1

An 11-year-old Hispanic male was referred to our psychiatric clinic because of nonadherence after a liver transplant attributable to extrahepatic biliary atresia when he was 4 years old. At the time of presentation, this patient had already been admitted several times because of episodes of rejection secondary to nonadherence. A psychiatric evaluation revealed that the patient was suffering from recurrent intrusive thoughts and dreams of his liver disease and the transplant, to the point that he was unable to perform his schoolwork because of frequently distracting thoughts about his illness. He also com-

plained of feeling anxious and his mother reported that he was irritable and jumpy. The patient said that he was trying to avoid any reminder of his liver disease, including being reluctant to come to clinic visits and not wanting to look at the abdominal scar. He did not talk to anyone, family and friends included, about his disease because he was “trying to not think about it,” although he said that he wished he could tell the whole world “what it is like.” These symptoms existed for more than a year and most were not noticed by the mother before the evaluation. Although nonadherence was the chief reason for referral, a decision was made to address the above transplant-related PTSD symptoms first, and therefore, adherence was not mentioned throughout the course of treatment. The patient and his family were seen for 10 consecutive weekly sessions. Individual sessions with the child focused on cognitive remodeling of his beliefs regarding the transplant (including his feelings of lack of mastery over his medical illness). Further, the patient was asked to talk about his fears to a video camera, and the recorded interview was played to him in sessions and eventually shown to his mother, providing a way of controlled reexposure to the stress as delineated in the patient’s own words. Finally, the patient was escorted by the therapist to a visit of the pediatric inpatient floor, where he spent his first few days following the transplant. At the end of these sessions, when the mother was asked about improvement, she stated that the patient is “definitely feeling better.” When asked about indicators of improvement, she immediately stated that he is now taking his medications as prescribed, although, as stated above, nonadherence was never directly addressed in treatment. This patient became adherent to his medication regimen, did not need rehospitalization for 9 months after the short course of treatment (whereas before that he was admitted 3 times over a period of 5 months) and is currently doing well.

Case 2

An 8-year-old white female was referred to psychiatric evaluation because of uncontrolled temper tantrums in a previously nonaggressive child, 3 months after an emergency liver transplant attributable to fulminant hepatic failure caused by Wilson’s disease. This patient had been in encephalopathic coma for 2 days after her transplantation but regained full mastery of her cognitive abilities. The parents complained of mood swings and irritability. The patient herself, although, stated that she suffered from recurrent disturbing dreams about dismemberment and in the first few sessions engaged in repetitive aggressive play with a recurrent theme of tearing up the mid-part (abdomen) of rival puppets. She stated that she is afraid of “almost anything” and avoided discussion of her illness. She initially complained of nausea whenever she had to take her medications, and her parents reported nonadherence. A diagnosis of transplant-related PTSD with a possible co-morbid mood disorder was made. Treatment in this case consisted of modeling through play and slow introduction of stressful themes in sessions

(eg, introduction of a doctor puppet in play). The patient became adherent as her play themes became more varied, concurrent with cessation of the bad dreams. However, although adherence was restored, medications eventually had to be introduced to control mood swings (Lithium was effective).

Case 3

This 19-year-old Hispanic female was referred for psychiatric consultation a few days after a second liver transplant. The first transplant was lost attributable to nonadherence—the patient did not come to clinic visits and did not take her immunosuppressant medications as prescribed for more than a year. She presented to the liver clinic in hepatic failure, already with mild encephalopathy, stating that she was interested in a second transplant and that she would adhere to recommendations from now on. However, several days after the second transplant, while still an inpatient, she stopped taking her medications again. When the therapist entered the room, the patient all but ignored him. However, when asked about specific symptoms, she warmed up and revealed that she had been suffering for more than 1 year from recurrent intrusive thoughts about her liver disease, and recurrent specific dreams about her wait for the first transplant. She reported being irritable and said that she wants to avoid any reminder of her illness, including even the sight of a nurse or a medication. The treatment in this case consisted of challenging her sense of low mastery over her disease, and a gradual exposure to the hospital environment (including allowing relatives to come visit and decorate her room on the unit so that it does not look like a hospital room). Family intervention was initiated, seeking to tighten the patient's social support network. As the patient's anxiety abated, she resumed taking her medications. She is currently (more than a year after the second transplant) adherent, and states that she no longer has the recurrent dreams, but she still feels irritable whenever she visits the pediatric liver clinic.

DISCUSSION

Our results point to a significant association between the concomitant existence of all 3 symptom clusters (and, particularly, the avoidance dimension) of PTSD and clinical nonadherence, as determined by a clinician panel and medication blood levels, in a sample of pediatric liver transplant recipients. Case histories detailing the course of management of 3 patients who benefited from a cognitive-behavioral approach to the treatment of transplant-related PTSD symptoms suggest that the clinical importance of this association could be substantial. Although not all nonadherent patients will turn out to be suffering from PTSD, even a moderately successful approach to the treatment of this condition would be important in terms of both patients' lives and expenditure.

One limiting aspect of any adherence study is the lack of a gold standard for the measurement of adherence.¹² We chose to use a clinician panel for the determination of nonadherence to assess the clinical significance of nonadherence in these patients. A

panel determination is not entirely independent of the medication blood levels—the clinicians were following these levels and may have based their determinations, in part, on these measures. The panel's determinations, however, were certainly not entirely based on blood levels as evident from the less than perfect match between the SD and panel decisions (see Table 1). In our sample, perfect agreement between raters was achieved when the question was specifically phrased as “the most severe cases.” Nonadherence in this study population, in our opinion, is best viewed as a continuum, with less clinical significance at the milder range. Clinician determinations of the whole spectrum are not reliable. However, the agreement among our raters about the most severe cases points to consistency of assessment. In a recent review of different methods to detect nonadherence in transplant recipients, both clinicians' reports and medication blood levels were reported to underestimate the rate of nonadherence, although their profiles of strengths and weaknesses were complementary,¹² which makes an assessment based on both of them a rational choice. For the purposes of the present study, this underrepresentation is acceptable, because we are interested in the extreme cases only and their relationship to PTSD, and not in a detection of nonadherence in general. In summary, no gold standard has been proven for assessment of nonadherence. The methods used in this retrospective assessment are not free of bias. However, the use of 2 different methods addressing a long-term pattern of nonadherence (and not a particular point of time determination), the demonstration of the effectiveness of a treatment approach in selected cases, and focusing on the most severe cases lend clinical significance to the reported results. This is a retrospective evaluation, and a larger prospective study would be needed for a more extensive assessment of the nature of the reported association.

Questionnaire criteria describe 3 groups of patients: “no PTSD” (only 1 cluster is represented or none at all), “partial PTSD” (2 of 3), and “full PTSD” (all 3 clusters represented). However, our patient population seemed to be better divided into only 2 groups: “full PTSD” and the rest. No significant differences were found between the “partial” and “no PTSD” groups. This categorical difference supports the threshold approach of the current PTSD diagnostic criteria. (The presence of all 3 symptom clusters is required to meet full DSM-IV diagnostic criteria. If only 2 of 3 are met, the diagnosis cannot be made. “Partial PTSD” does not exist in the current classification scheme.)

It is not surprising that parents tended to underestimate the symptoms of their children. A discrepancy between parental and children's reports of PTSD symptoms in a pediatric population was previously documented.^{16,17} It may represent denial and avoidance on the part of the parents, so that they could escape the discomfort of the traumatic experience that they themselves experience.¹⁸ This observation underscores the importance of direct interviews with affected children, not only with caretakers, during posttransplant evaluations.

Our sample is small, and the number of nonadherent patients is not enough to rule out some sociodemographic differences and other potential confounding variables. However, others previously noted that no consistent relationship between adherence and sociodemographic factors was shown to exist in the pediatric population.^{4,19} The observation that all the patients who were clinically nonadherent were classified as “full PTSD” seems to suggest that only patients who suffer from symptoms of PTSD are nonadherent. This striking result is probably an artifact of the small sample size (we hypothesize that some, not all, cases of nonadherence may be related to symptoms of PTSD).

Some of the factors that are associated with nonadherence to medical management, such as less supportive families,²⁰ are also associated with PTSD in children.²¹ Therefore, it is possible that PTSD symptoms are a manifestation of the same factors that lead to nonadherence, and not a cause of it. If this is the case, determination of PTSD symptoms could aid in detection of nonadherence and monitoring the progress of its treatment. Our clinical experience suggests, however, that addressing PTSD symptoms in our population improves adherence. This phenomenon was previously described in a series of burn patients.²² This observation suggests that symptoms of PTSD actually lead to nonadherence and are not only associated with it. According to this formulation, some patients who suffer from serious life-threatening illnesses are traumatized in a similar fashion to war veterans. These patients avoid reminders of their condition, because thinking about their disease is painful and provokes anxiety. Medications serve as such reminders. Therefore, treatment of the associated symptoms may restore adherence in this population, as indeed was demonstrated in the case reports. The treatment of PTSD in children is not well established. However, a cognitive-behavioral approach was previously described as helpful.¹⁵ The efficacy of this approach was further suggested by our own experience, as described.

The finding that only a minority of our patients reported symptoms from all 3 domains of PTSD underscores the importance of recognizing that PTSD is just 1 of many possible forms of response to a traumatic event.²³ The association with nonadherence may make it especially important to recognize and treat this particular response.

CONCLUSION

In summary, we describe a novel concept that explains nonadherence in some patients and may have interesting therapeutic implications. It remains to be determined whether PTSD symptoms are manifestations of the same underlying factors that predispose to nonadherence or whether other independent factors lead to it. A causal relationship is suggested, but not proven by, the reports made by us and others²² that nonadherence resolves concurrently with the treatment of PTSD. In either case, the diagnosis, treatment, and continuous assessment of post-traumatic symptoms are probably warranted. This report deals with pediatric liver transplant recipi-

ents. We believe that this concept may be applicable to other groups of patients and we are currently investigating this hypothesis. However, others have cautioned against the application of the concept of medical disease-related PTSD to populations of patients who do not suffer from an acute, definable, and life-threatening stressor.²⁴ We believe that, indeed, this model should not automatically be applied to diseases such as diabetes, in which an extreme, life-threatening event may not be present. Our current sample is small, and final conclusions should be deferred until more data are available. Some methodological difficulties encountered in this initial retrospective representation of a novel phenomenon can be addressed in future prospective assessment of PTSD in this and other populations.

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