International Journal of Pediatric Otorhinolaryngology (2003) **67**, 151–155

International Journal of Pediatric Otorhinolaryngology

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Risk factors for adenotonsillar hypertrophy in children following solid organ transplantation☆

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Received 18 July 2002; received in revised form 5 September 2002; accepted 8 September 2002

KEYWORDS
PTLD;
Epstein-Barr virus;
Adenotonsillar hypertrophy

Summary *Objective:* Post-transplantation lymphoproliferative disorder (PTLD), or its precursor, Epstein-Barr virus (EBV)-related lymphoid hyperplasia, may first present in the tonsils and adenoids in the pediatric solid organ transplant population. We sought to identify signs and symptoms of and risk factors for adenotonsillar hypertrophy (ATH), a potential precursor to PTLD in children following solid organ transplantation. *Methods:* We performed a cross-sectional study of 132 consecutive pediatric solid organ transplant patients at our institution. Questionnaire, physical examination, and laboratory data collection were obtained. Correlation of signs and symptoms of ATH with objective laboratory data was conducted. *Results:* 132 pediatric transplant recipients (64 renal, 68 liver) were enrolled. Mean age at transplantation was 7.4 (S.D. 6.0) years with a mean follow-up of 49.0 (S.D. 48.4) months post-transplantation. The mean questionnaire score was 8.4 (S.D. 7.9) out of a maximum 65 and the mean physical examination score was 3.9 (S.D. 1.9) out of a maximum 8, with a statistically significant correlation between the two (Pearson's $r = 0.352$, $P < 0.001$). A multivariate linear regression model found recipient EBV seronegativity and younger age at transplantation to be statistically significant risk factors for development of ATH ($P = 0.024$ and 0.035, respectively). *Conclusions:* Young age and EBV seronegativity confer increased risk for ATH in pediatric patients undergoing solid organ transplantation. As ATH may be the earliest sign of PTLD, long-term surveillance is required to determine the impact of ATH on quality of life and survival in these patients.

1. Introduction

With the advent of more potent immunosuppressant medications, long-term survival of organ transplant recipients has markedly risen. However, we are now faced with a concomitant increase in long-term complications arising from immunosuppressant use. Post-transplantation lymphoproli-

☆ Presented at the American Society of Pediatric Otolaryngology, 16th Annual Meeting, Scottsdale, Arizona, May 11, 2001.

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PII: S0165-5876(02)00356-7

ferative disorder (PTLD), a potentially organ-threatening, or life-threatening, disorder of the lymphoreticular system, may present in its earliest form as adenotonsillar hypertrophy (ATH). However, it is not yet known what specific risk factors exist in this population for developing ATH, and potentially PTLD. We sought to identify possible associations between objective and subjective data that may point to distinct risk factors for ATH in this population. By identifying such risk factors, more focused screening protocols may be established to allow for early identification of patients at risk for PTLD and thereby promote its prevention. With long-term surveillance, quantitative parameters for early intervention may be established.

PTLD represents a spectrum of disorders involving abnormal lymphoid cell proliferation [1]. It is associated with Epstein-Barr virus (EBV) in 80% in the setting of immunosuppression [2]. Adenotonsillar tissue is often a reservoir for replicating EBV, and may enlarge secondary to EBV proliferation, leading to EBV-related lymphoid hyperplasia. EBV-related lymphoid hyperplasia is a known precursor to PTLD. Recent studies have identified a predominance of EBV-associated lymphoid hyperplasia in tonsil and adenoid tissue of post-transplantation children [3–5].

2. Subjects and methods

The subjects of this report are pediatric liver and kidney transplant recipients who were seen at the University of California, Los Angeles Pediatric Liver and Kidney Transplantation Program Clinics over a 4-week period. All patients presented for routine post-transplantation follow-up, and were invited to participate in this cross-sectional analysis of signs and symptoms of ATH during their transplantation clinic visit. Institutional Review Board approval (IRB # 99-10-010-01) was obtained prior to initiation of this study.

2.1. Transplantation history

Medical records regarding type and number of organs transplanted, indication for transplantation, age at time of transplantation, pre-transplantation EBV serology, and current immunosuppressant use were reviewed. Pre-transplant EBV serology was based on the following values for antibody titers at our institution: EBV–viral capsid antigen (VCA) IgM $<$ 1:20 = EBV seronegative; EBV–VCA IgM $>$ 1:20 = EBV seropositive; EBV–VCA IgG $<$ 1:10 = EBV seronegative, EBV–VCA IgG $>$ 1:10, $<$ 1:640 = EBV equivocal; EBV–VCA IgG $>$ 1:640, or fourfold increase in antibody titer = EBV seropositive. EBNA (Epstein-Barr nuclear antigen) $<$ 1:5 = EBV seronegative, EBNA $>$ 1:5 = EBV seropositive.

2.2. Clinical signs and symptoms

Symptoms referable to ATH were elicited and quantified with a structured questionnaire (Fig. 1). This questionnaire was adapted from the obstructive sleep apnea-18—item questionnaire, a valid and reliable measure of symptoms of obstructive sleep disorder secondary to ATH [6]. Since our patient population was limited to children with chronic illness, questions such as those related to school and activities missed and overall health, were purposely omitted during adaptation to make it more applicable to this patient population. Signs of ATH were evaluated by grading tonsil size on a scale of 1 to 4 (1, endophytic tonsils, anterior and posterior pillars visible; 2, tonsils extend to tonsillar pillars; 3, tonsils extend beyond tonsillar pillars, approximating uvula; 4, tonsils apposing each other; or tonsillar asymmetry). Visualizing open- or closed-mouth breathing at rest, engorged nasal mucosa, or evidence of rhinorrhea assessed adenoid enlargement (Fig. 2). Clinical signs and symptoms were then correlated to objective medical record data Statistical analysis was conducted with SPSS version 10.0 (Chicago, IL). Univariate analysis was conducted comparing exam score and questionnaire score between groups using ANOVA. Mean questionnaire scores and examination scores were evaluated with regard to type of transplant received, age at transplant, and recipient EBV serology at the time of transplant. Multivariate linear regression was conducted to determine predictive factors for elevated questionnaire and physical examination scores in this patient population.

3. Results

One hundred and thirty-two patients were evaluated. Sixty-four had received kidney transplantation, and 68 had received liver transplantation. Mean age at transplantation was 7.4 (S.D. 6.0) years, with a mean follow-up of 49.0 (S.D. 48.4) months post-transplantation. The mean questionnaire score for all patients was 8.40 (S.D. 7.9), out of a maximum score of 65 points. The mean physical examination score for all patients was 3.90 (S.D. 1.90), out of a maximum score of 8 points. The correlation between the mean ques-

How often does your child snore?
Never (0) Rarely (1) 1-4 times/month (2) More than once a week (3) Most nights (4)
How loud is the snoring?
No snoring (0) Mild/quiet (1) Medium loud (2) Loud (3) Extremely loud (4)
Does your child awaken in the middle of the night?
Never (0) Rarely (1) 1-4 times/month (2) More than once a week (3) Most nights (4)
Does your child wet the bed?
Never (0) Rarely (1) 1-4 times/month (2) More than once a week (3) Most nights (4)
Do you ever see your child struggling to breathe during sleep? Yes (4) No (0)
Do you ever see your child stop breathing during sleep? Yes (4) No (0)
When your child is asleep, do you ever shake him or her to start breathing again?
Yes (4) No (0)
Do you ever see your child's lips or skin turn blue or purple during sleep?
Yes (4) No (0)
Do you ever watch your child while he or she is asleep at night, afraid of his or her breathing? Yes (4) No (0)
How often does your child have a sore throat?
Never (0) Rarely (1) 1-4 times/month (2) More than once a week (3) Almost daily (4)
How often does your child have sinusitis?
Never (0) Rarely (1) 1-4 times/month (2) More than once a week (3) Almost daily (4)
Does your child complain of morning headaches?
Never (0) Rarely (1) 1-4 times/month (2) More than once a week (3) Almost daily (4)
Is your child a daytime mouthbreather?
Never (0) Rarely (1) Frequently (2) Constantly (3)
Does your child have a problem with daytime sleepiness?
None (0) Slight (1) Moderate (2) Considerable (3) Very great (4)
Does your child have a problem with daytime hyperactivity?
None (0) Slight (1) Moderate (2) Considerable (3) Very great (4)
Does your child ever choke when eating solid food?
Never (0) Rarely (1) Frequently (2) Constantly (3)
Does your child ever choke when drinking liquids?
Never (0) Rarely (1) Frequently (2) Constantly (3)

(Maximum score: 65)

Fig. 1 Parental questionnaire.

Quiet respiration:

Mouth closed (0) Mouth open (1)

Intraoral examination:

Tonsils:

1+ (endophytic tonsils, anterior and posterior pillars visible) (1)

2+ (tonsils extend to tonsillar pillars) (2)

3+ (tonsils extend beyond tonsillar pillars, approximating uvula) (3)

4+ (tonsils approximating each other in the midline) (4)

Tonsillar asymmetry (4)

Intranasal examination:

Normal inferior turbinates/ no discharge (0)

Edematous inferior turbinates (2)

Clear rhinorrhea (2)

Mucopurulent discharge (3)

(Maximum score: 8)

Fig. 2 Physical Examination.

tionnaire score and mean physical examination score was statistically significant (Pearson's $r = 0.352$, $P < 0.001$). The mean questionnaire score for kidney transplant recipients was 8.03 (S.D. 8.09), and the mean questionnaire score for liver transplant recipients was 8.68 (S.D. 7.84). These differences were not statistically significant. Similarly, there was no statistically significant difference in mean physical examination scores for kidney and liver recipients 3.69 (S.D. 2.09) and 4.02 (S.D. 1.71) for kidney and liver recipients respectively (Table 1). At the time of transplant among 132 subjects, 60 patients were EBV seropositive, 50 were EBV seronegative, and 22 patients demonstrated equivocal serology. Patients with the equivocal serologies were treated as missing values for the subsequent analysis. Multivariate linear regression analysis revealed that younger age at transplantation and EBV seronegativity of the transplant recipient at the time of transplantation were statistically significant risk factors for demonstrating signs of ATH ($P = 0.024$ and 0.035, respectively). On multivariate analysis, we were unable to identify any clinical variables that predicted higher questionnaire scores (all $P > 0.05$).

Clinical variables that were not found to be significant predictors of ATH included gender,

Table 1 Summary of mean questionnaire and physical exam scores for kidney and liver transplant recipients

	n	Mean	Standard deviation
Questionnaire score (max 65)			
Total subjects	132	8.40	7.90
EBV seronegative	50	9.26	7.70
EBV seropositive	60	7.38	7.59
Kidney recipients	58	8.03	8.09
Liver recipients	62	8.68	7.84
Physical examination score (max 8)			
Total subjects	132	3.90	1.90*
EBV seronegative	50	4.44	1.66
EBV seropositive	60	3.30	1.90
Kidney recipients	58	3.69	2.09
Liver recipients	62	4.02	1.71

* $P < 0.001$.

follow-up duration from transplant, type of organ transplanted, donor source for transplanted organ, CMV status of the transplant recipient, or the use of immunosuppressant medications (tacrolimus, cyclosporine, or prednisone) (Table 2).

4. Discussion

PTLD is a potentially devastating illness in the pediatric solid organ transplant population. Several studies have sought to identify risk factors for this disease, including EBV serology [7], CMV serology [8], type of organ transplanted [9], and type and dosage of immunosuppressant medications [10]. Association between recipient EBV seronegativity and risk for PTLD has been recognized [10]. This is in keeping with the concept that EBV-related hyperplasia is a precursor to PTLD, and that the EBV seronegative recipient, once immunosuppressed, may develop acute EBV infection from either the EBV seropositive donor or from environmental exposure. In the setting of immunosuppression, this EBV infection may lead to uncontrolled proliferation of B-lymphocytes, resulting in PTLD [1,11,12]. Several studies have demonstrated that adenotonsillar tissue is a principal reservoir for EBV replication, and EBV-related lymphoid hyperplasia is frequently found in adenotonsillar tissue after removal [3–5,13,14]. Transplant centers are now monitoring early EBV proliferation by serially following EBV-polymerase chain reaction levels during routine post-transplantation blood levels [7,15].

Table 2 Summary of multivariate linear regression analysis coefficients and statistical significance for the prediction of ATH

Variable	Multivariate significance	Linear regression coefficient
EBV Seronegativity	0.035	−0.876
Age at transplantation	0.024	−0.061
Male gender	0.719	NS
Months post-transplantation	0.140	NS
Type of organ transplanted	0.304	NS
Donor source for transplanted organ	0.494	NS
Recipient CMV status	0.212	NS
Tacrolimus use	0.265	NS
Prednisone use	0.694	NS

NS, Not significant.

PTLD, or its precursor, EBV-related lymphoid hyperplasia [16], may first present in the tonsils and adenoids in the pediatric solid organ transplant population [17]. As such, we sought to identify potential risk factors for ATH in this population. By doing so, prompt adenotonsillectomy may initiate management of PTLD in its earliest forms. Treatment of localized PTLD or EBV-related lymphoid hyperplasia may also include mild alteration in immunosuppressant regimens. Treatment of fulminant PTLD with multi-organ system involvement may require complete cessation of immunosuppressant medications and institution of chemotherapy, putting the patient at risk of organ loss or death.

Our data revealed that young age at the time of transplant and EBV-seronegativity at the time of transplant conferred increased risk of both signs

and symptoms of ATH, according to our questionnaire and physical exam scores. These results are in keeping with previous reports [14]. It is logical that a younger patient would be more likely to be EBV seronegative; younger patients are less likely to have been exposed to EBV to allow for seroconversion than older patients. Although younger age at transplantation and EBV seronegativity are likely to be linked in the pediatric population, they were found to be independent predictors of ATH in the multivariate regression model. A multivariate regression analysis was conducted because of the cross-sectional nature of this investigation with a time-dependent variable. In addition, multivariate analysis allowed for the examination of multiple variables simultaneously, which is necessary in a cross-sectional analysis.

It is somewhat surprising that time elapsed from transplant would not be associated with increased incidence of ATH, as these patients have had longer duration of exposure to immunosuppressants, and potential for developing lymphoid enlargement. We also did not find any association between type of immunosuppressant use and ATH. Previous studies have demonstrated higher incidence of PTLD with more potent immunosuppressants such as OKT3 and tacrolimus [9]. There were several limitations to this study. First, since all patients were evaluated during post-transplantation visits, radiographic or endoscopic analysis of the adenoids directly was not feasible in this clinical setting. Second, we did not have access to patients prior to transplantation, which would have allowed for better follow-up of any potential changes in adenotonsillar signs or symptoms after initiation of immunosuppressant therapy. A study including these parameters will be planned at our institution in the near future.

While there is no definitive association between ATH and PTLD, it is known that PTLD may present as ATH, [5,17] or, rarely, as upper airway obstruction at a site other than Waldeyer's ring [18]. By identifying risk factors for ATH, we may be able to develop screening protocols for tonsil and adenoid monitoring in this patient population. By continuing to monitor these patients, our long-term goal is to develop preemptive management of tonsils and adenoids in children at risk for developing PTLD.

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