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The validity of the OSA-18 among three groups of pediatric patients☆

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Summary

Objective: To compare the signs and symptoms of obstructive sleep apnea syndrome in three groups of pediatric patients; solid organ transplant recipients, healthy children, and children with leukemia; in order to examine the effects of chronic illness on the obstructive sleep apnea—18-item questionnaire and to investigate its validity as a screening tool for obstructive sleep apnea in the pediatric solid organ transplant population.
Methods: In this cross-sectional study, there were two hundred and six subjects; 46 kidney transplant recipients, 59 liver transplant recipients, 34 patients with leukemia, and 67 healthy children. Adenotonsillar enlargement was assessed by using the obstructive sleep apnea—18-item questionnaire and by performing a focused physical examination of the oral and nasal cavity at the time of the child's routine visit in either the transplant clinic, outpatient oncology center, or general pediatric clinic.
Results: Comparison of questionnaire scores amongst the three groups showed significant differences between the healthy children and liver transplant recipients as well as those with leukemia. There was a significant difference in the physical examination scores of the children with leukemia as compared to the other groups.
Conclusions: Adenotonsillar enlargement in pediatric transplant recipients can be an early indication of post-transplantation lymphoproliferative disorder. However, the prevalence of adenotonsillar enlargement in the transplant population does not appear to differ from that of the healthy population. Additionally, scores on the

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OSA-18 in the transplant population were confounded by chronic illness. Further prospective studies need to be performed to develop a screening tool to identify transplant recipients at risk for post-transplantation adenotonsillar lymphoma.

1. Introduction

Adenotonsillar enlargement in the healthy pediatric population has been attributed to recurrent upper respiratory tract infections and allergy-related upper respiratory tract inflammation [1]. Adenotonsillar enlargement in the post-transplant population may be a result of the same processes as seen in healthy children; however it may also be indicative of post-transplantation lymphoproliferative disorder (PTLD) [2].

Post-transplantation lymphoproliferative disorder is defined as an abnormal proliferation of lymphocytes, symptoms of which may include fever, poor appetite, weight loss, irritability and generalized malaise [3—6]. Conversely, the patient may be asymptomatic and present solely with enlarged tonsils and adenoids. PTLD has been attributed to Epstein—Barr virus (EBV) infection in up to 80% of cases; EBV hyperplasia in adenotonsillar tissue may represent an early stage of PTLD. EBV, a ubiquitous herpes virus, infects and immortalizes B-lymphocytes, with the epithelial cells of Waldeyer's ring as a primary site of replication [7]. The immunocompetent host launches a T-lymphocyte response to control the proliferation of B-lymphocytes, following EBV infection. The anti-T-lymphocyte specific immunosuppressant agents utilized following solid organ transplantation limit the T-lymphocyte response, allowing uncontrolled proliferation of B-lymphocytes [2,8—11].

The prevalence of adenotonsillar enlargement in the pediatric post-transplantation population, relative to the general pediatric population, remains unknown.

Adenotonsillar enlargement may be more prevalent in the transplant population, secondary to EBV infections in the setting of immunosuppression. Using the obstructive sleep apnea syndrome—18-item questionnaire (OSA-18) and a focused physical examination to identify children with adenotonsillar enlargement, this study compared the prevalence of signs and symptoms of adenotonsillar enlargement between solid organ transplant recipients, children with chronic illness, and healthy subjects. Children with leukemia were studied as a control group to examine the effect of chronic and life-threatening illness on OSA-18 scores. Our objective is to identify adenotonsillar enlargement in those children at risk for PTLD, allowing for earlier diagnosis and treatment of this organ-threatening and life-threatening disorder.

2. Subjects and methods

The subjects of this study were pediatric patients at the Mattel-UCLA Children's Hospital, between January 2002 and August 2002. Three groups were studied; pediatric solid organ transplant recipients, children with leukemia, and healthy children. The children were examined in the general pediatrics clinic, the oncology clinic or the respective transplant clinic. These children were being seen for routine care and were not seeking treatment for possible airway obstruction, upper respiratory disorders, or sleep disorders. Approval for the study was obtained from the medical institutional review board of the University of California, Los Angeles Office for the Protection of Human Research Subjects (IRB 99-10-010-02).

Abstraction of the medical records allowed for relevant past medical history to be obtained for each subject. For the transplantation recipients, this included type of organ transplant, age at transplantation, Epstein—Barr virus (EBV) serology of donor and recipient, immunosuppressant medications, and history of organ rejection. For the children with leukemia, this included type of chemotherapeutic agent, date of last treatment cycle, and history of bone marrow transplantation. For the healthy children, history of mononucleosis and any medical problems were recorded.

For the transplantation group, all kidney and liver transplant recipients under 21 years of age were invited to participate. The exclusion criterion was prior adenotonsillectomy. For the children with leukemia, inclusion criteria consisted of current use of chemotherapy and exclusion criteria were completion of chemotherapy greater than 6 months prior to the time of study enrollment, and history of adenotonsillectomy. For the healthy population, children under 21 years of age were eligible. Exclusion criteria included those children with prior adenotonsillectomy, current respiratory infection, chronic heart disease, and chronic lung disease, including asthma, bronchopulmonary dysplasia or cystic fibrosis.

3. Intervention

During the patient's scheduled outpatient clinic visit, the parent or guardian was invited to have their child participate in the study. The obstructive sleep apnea syndrome—18-item questionnaire (OSA-18) was administered and a focused physical examination of the patient's nasal and oral cavities was performed. The OSA-18 was divided into five sections, assessing sleep disturbance, physical symptoms, emotional distress, daytime function, and caregiver concerns (Table 1) [12]. The physical examination was divided into three parts; quiet respiration through the mouth or nose, examination and grading of the size of the tonsils, and examination of the inferior turbinate size and nasal discharge as an indicator of adenoid-related nasal airway obstruction (Table 2).

4. Outcome

The results of the questionnaire and physical examination were compared between the three groups, accounting for confounding variables such as age, height, weight and type of organ transplant. Transplant recipients with OSA-18 scores greater than 80 or physical examination scores greater than three were referred for possible adenotonsillectomy, due to the increased risk of post-transplantation lymphoproliferative disorder in these patients. Any child with an OSA-18 score greater than 80 out of a maximum 126 was referred for evaluation by a pediatric otolaryngologist. According to Franco et al. [12], an OSA-18 score of 80 or greater correlated with severe obstructive sleep apnea syndrome with a significant impact on health-related quality of life. Children with asymmetric tonsils in any group

Table 1 Obstructive Sleep Apnea Syndrome Quality of Life Survey (OSA-18) [1]

None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
1	2	3	4	5	6	7

Sleep Disturbance

During the past 4 weeks, how often has your child had...
...loud snoring?
...breath holding spells or pauses at night?
...choking or made gasping sounds while asleep?
...restless sleep or frequent awakenings from sleep?

Physical Symptoms

During the past 4 weeks, how often has your child had...
...mouth breathing because of nasal obstruction?
...frequent colds or upper respiratory infections?
...nasal discharge or a runny nose?
...difficulty in swallowing food?

Emotional Distress

During the past 4 weeks, how often has your child had...
...mood swings or temper tantrums?
...aggressive or hyperactive behavior?
...discipline problems?

Daytime Function

During the past 4 weeks, how often has your child had...
...excessive daytime sleepiness?
...a poor attention span or concentration?
...difficulty getting up in the morning?

Caregiver Concerns

During the past 4 weeks, how often have the problems described above...
...caused you to worry about your child's general health?
...created concern that your child is not getting enough air?
...interfered with your ability to perform daily activities?
...made you frustrated?

MAXIMUM SCORE: 126

Table 2 Physical Examination Grading Scale

Quiet Respiration:		
Mouth closed (0)	Mouth open (1)	
Oronasal 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 apposing each other, obliterating visualization of uvula	(4)
other	tonsillar asymmetry	(4)
Nose:		
1	normal turbinates/no discharge	(0)
2	edematous turbinates	(2)
3	clear rhinorrhea	(2)
4	mucopurulent drainage	(3)

were also referred to a pediatric otolaryngologist to evaluate for tonsillar lymphoma.

5. Results

Two-hundred and six children participated in this study from January 2002 to August 2002. Forty-six patients had received kidney transplants, 59 patients were liver transplant recipients, 34 patients had leukemia, and 67 were healthy children. Liver and kidney transplant recipients were considered as two separate groups, as the risk for PTLD has been shown to be greater in liver transplant recipients than in kidney transplant recipients [15].

The healthy children had a mean age of 4.3 years. The mean ages for the kidney transplant recipients and the liver transplant recipients were 14.5 and 10.4 years, respectively. The children with leukemia had a mean age of 9.7 years. When the mean ages of the groups were compared, there were statistically significant differences between all groups, except between the children with leukemia and the liver transplant recipients. This difference can be explained by the fact that younger children visit the general pediatric clinic more frequently than older children, and that the transplant and oncology centers care for older children and follow them into adulthood. However, no correlation existed between age and physical examination scores or OSA-18 scores, in any group or for the study participants as a whole.

The mean OSA-18 score for the healthy children was 29.52, out of a maximum of 126. The mean score for kidney transplant recipients was 32.98, and 34.03 for liver transplant recipients. Children with leukemia had a mean score of 33.79. Although there was no statistically significant difference when mean scores were compared, Kruskal—Wallis test of medians showed a statistically significant difference between the median scores for the healthy children and the liver transplant population ($p = 0.011$), as well as a difference between the children with leukemia and healthy children ($p = 0.037$) (Table 3).

In order to examine where the differences exist within the questionnaire, the five components of OSA-18 were analyzed separately. No statistically significant differences were noted between the populations in the categories of sleep disturbance, physical symptoms, or caregiver concern. However, both the mean and median score for emotional distress were significantly higher for liver transplant recipients when compared to healthy children ($p = 0.015$ and 0.005, respectively). A statistically significant difference existed in the median scores in daytime function of both kidney ($p = 0.005$) and liver ($p = 0.017$) transplant recipients when compared to healthy children. A difference, although not statistically significant, also existed in daytime function between children with leukemia and healthy children ($p = 0.064$) (Table 4).

The mean physical examination score for healthy children was 2.40 out of a maximum of 8. Kidney transplant recipients had a mean physical examination score of 2.87 and liver transplant recipients had a mean score of 2.86. The mean score of the children with leukemia was 1.88. While there was no statistically significant difference in physical examination

Table 3 Mean and median questionnaire and examination scores

	Mean age (years)	OSA-18 mean score (max 126)	OSA-18 median score (max 126)	Physical examination mean score (max 8)	Physical examination median score (max 8)
Healthy children	4.3	29.52	24	2.40	2
Liver transplant	10.4	34.03	29	2.86	3
Kidney transplant	14.5	32.98	30	2.87	2
Leukemia patients	9.7	33.79	30	1.88	2

Table 4 *p*-values from Kruskal—Wallis test of medians for comparison of OSA-18 scores between study populations

	OSA-18 total	Sleep disturbance	Physical symptoms	Emotional distress	Daytime function	Caregiver concerns
Healthy vs. liver transplant	**0.011**	0.612	0.069	**0.005**	**0.017**	0.303
Healthy vs. kidney transplant	0.113	0.450	0.194	0.198	**0.005**	0.132
Healthy vs. leukemia patients	**0.037**	0.705	0.133	0.144	0.064	0.322
Leukemia vs. liver transplant	0.978	0.915	0.915	0.348	0.756	0.917
Leukemia vs. kidney transplant	0.726	0.693	0.630	0.806	0.398	0.823
Liver vs. kidney transplant	0.576	0.634	0.666	0.216	0.500	0.637

p-values <0.05 represent statistically significant differences between groups.

scores between healthy children and children who had received solid organ transplants, a statistically significant difference existed when children treated for leukemia were compared to both the healthy population and the organ transplant recipients. Both the mean and median physical examination scores were significantly higher for liver transplant recipients ($p = 0.001$ and 0.002, respectively) and for kidney transplant recipients ($p = 0.002$ and 0.001, respectively) when compared with the patients with leukemia. Healthy children also had significantly higher median physical examination scores relative to children treated for leukemia ($p = 0.009$) (Table 5).

6. Discussion

Adenotonsillar enlargement is common in the pediatric population, and adenotonsillar tissue often regresses as the child matures. In the general pediatric population, this phenomenon has been attributed to chronic upper respiratory tract illness or allergic upper respiratory tract inflammation. Adenotonsillar enlargement is of concern when it is associated with symptoms of upper airway obstruction. This, in turn, may result in obstructive sleep apnea.

Adenotonsillar enlargement in pediatric solid organ transplant recipients may have other causes and consequences. Adenotonsillar enlargement has been shown to be an early indicator of post-transplantation lymphoproliferative disorder (PTLD) in the transplant population [13]. PTLD includes a spectrum of lymphatic proliferation, ranging from asymptomatic lymphadenopathy to lymphoma. A suspected precipitant of PTLD is EBV infection in the setting of immunosuppression. Epstein—Barr virus infects B-lymphocytes, resulting in proliferation and immortalization of these cells. In an immunocompetent host, T-lymphocytes suppress the proliferation of B-lymphocytes, limiting the infection and B-lymphocyte response. However, the immunosuppressant medications currently utilized to prevent rejection after transplantation specifically target T-lymphocytes. Without active T-lymphocytes, the B-lymphocytes continue to proliferate without restraint, and PTLD may develop. Adenotonsillar tissue from tonsillectomies performed on transplant recipients at our institution has shown EBV-related hyperplasia in up to 80% of cases [12,13]. Prior cross-sectional analysis of transplant recipients at Mattel-UCLA Children's Hospital has identified EBV seronegativity at the time of transplant as a risk factor for adenotonsillar enlargement [14,15]. One objective of this study was to develop a tool to identify adenotonsillar enlargement and therefore PTLD at an earlier stage.

The obstructive sleep apnea syndrome—18-item questionnaire (OSA-18) was intended to be a screening tool to identify children with obstructive sleep apnea. The questionnaire was composed of five

Table 5 Comparison of physical exam score between study populations

	p-value for difference in mean physical examination score	*p*-value for difference in median physical examination score
Healthy vs. liver transplant	0.059	0.147
Healthy vs. kidney transplant	0.075	0.115
Healthy vs. leukemia patients	0.071	**0.009**
Leukemia vs. liver transplant	**0.001**	**0.002**
Leukemia vs. kidney transplant	**0.002**	**0.001**
Liver vs. kidney transplant	0.985	0.976

p-values <0.05 are statistically significant.

domains: i.e. sleep disturbance, physical symptoms, emotional distress, daytime function and caregiver concerns; areas where obstructive sleep apnea had been shown to have an impact on quality of life. When Franco et al. [12] compared mean and total scores on the OSA-18 to sleep study scores, adenoid size, and tonsillar size, a positive correlation was demonstrated between the questionnaire and the three objective measures. In the healthy population, the OSA-18 has shown validity as a screening tool to grade the severity of obstructive sleep apnea syndrome. One goal was to determine if the OSA-18 would provide an adequate screening tool to identify adenotonsillar enlargement in the post-transplantation population. The OSA-18 utilizes daytime fatigue and problems with attention and behavior as some of the indicators of obstructive sleep apnea. Our concern was that discrepancies in these domains of the questionnaire could be difficult to interpret in the setting of a chronic illness, such as organ transplantation. Immunosuppressant medications, chronic illness, and adjustment difficulties after an extended hospitalization could certainly result in fatigue and behavioral problems. This could impact the significance of OSA-18 scores in this population. For this reason, it was decided to choose a control population with chronic illness to compare to healthy children and transplant recipients. Children suffering from leukemia incur potential problems related to their chronic illness and also receive medications which may cause fatigue, in addition to immunosuppression.

Differences in OSA-18 questionnaire scores were identified between healthy subjects and liver transplant recipients. There was also a difference in total OSA-18 questionnaire scores between children with leukemia and healthy children. The most significant differences in OSA-18 scores for the liver transplant recipients when compared to healthy children existed in the domains of emotional distress and daytime function. The differences in daytime function were also seen in children with leukemia. This finding demonstrates a limitation of the OSA-18 questionnaire in the chronically ill population. Many of the symptoms evaluated by the questionnaire may be secondary to chronic illness and not as the result of an obstructive sleep disorder secondary to adenotonsillar enlargement. The domains of emotional distress and daytime function had the lowest correlation with sleep study scores and adenotonsillar size in the original study by Franco et al. These categories were included in the OSA-18 item questionnaire as they had been described in earlier literature to be predictors of health-related quality of life. A questionnaire omitting questions related to emotional distress and daytime function may be a more appropriate screening tool for the transplant population.

This study also utilized physical examination of the oral and nasal cavities to identify adenotonsillar enlargement. No difference was noted in physical examination scores between the healthy children and the organ transplant recipients. However, a significant difference was noted between the children treated for leukemia and all three other populations. This finding may support the hypothesis that adenotonsillar enlargement results from B-lymphocyte proliferation after EBV infection. Epstein—Barr virus infects the adenotonsillar tissue of Waldeyer's ring, which is composed of the adenoids, palatine tonsils, and lingual tonsils. Adenotonsillar tissue enlarges as a result of B-lymphocyte hyperplasia. Although the children treated for leukemia are immunosuppressed, the medications that they receive suppress both B- and T-lymphocytes. This would reduce B-lymphocyte proliferation and induce regression of adenotonsillar tissue. Immunosuppressant medications for transplant recipients have been developed to selectively inhibit T-lymphocytes, therefore allowing uncontrolled B-lymphocyte proliferation, and continued adenotonsillar enlargement. This may explain the discrepancy in adenotonsillar size between the children treated for leukemia and the solid organ transplant recipients. Pathologic examination of adenotonsillectomy specimens from children treated for leukemia should be studied to determine if they have a low prevalence of EBV-related hyperplasia.

7. Conclusion

In otherwise healthy children, adenotonsillar enlargement has been attributed to chronic upper respiratory infections and allergy-related upper respiratory inflammation [2]. Management remains controversial, although adenotonsillectomy is an accepted treatment for obstructive sleep apnea secondary to enlarged tonsils and adenoids [16—18].

Adenotonsillar enlargement in the post-transplantation population appears to have greater significance, as a marker for EBV-related hyperplasia and PTLD. When identified either by symptoms or physical examination, recommendation for adenotonsillectomy should be emphasized. Unlike tonsils and adenoids of healthy children, which may be observed for regression, pathologic examination of adenotonsillar tissue is necessary to identify early lymphoproliferative disorders [12]. In the future, a comparison of the pathology specimens from adenotonsillectomy in the different populations could be performed to further establish the role of EBV

and B-lymphocyte proliferation in adenotonsillar enlargement.

The utility of the OSA-18 as a screening tool for identifying adenotonsillar enlargement in the post-transplantation population has yet to be determined. By our evaluation of other chronically ill patients, it appears that the effects of chronic illness confound the results of the OSA-18 questionnaire. A screening tool oriented toward the post-transplantation population, which does not include questions on emotional distress, should be developed to aid in the identification of adenotonsillar enlargement. Health care professionals caring for pediatric patients with solid organ transplants should continue vigilance in identifying the early signs and symptoms of adenotonsillar enlargement and post-transplantation lymphoproliferative disorder.

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