Published in final edited form as:

Laryngoscope. 2013 August ; 123(8): 2043–2049. doi:10.1002/lary.23748.

Deep cervical lymph node hypertrophy: a new paradigm in the understanding of pediatric obstructive sleep apnea

Sanjay R. Parikh, MD, FACS¹, Babak Sadoughi, MD², Sanghun Sin, MS³, Seth Willen, MD², Kiran Nandalike, MD³, and Raanan Arens, MD³

¹Department of Otolaryngology – Head and Neck Surgery, Seattle Children's Hospital -University of Washington School of Medicine

²Department of Otorhinolaryngology – Head and Neck Surgery, Children's Hospital at Montefiore – Albert Einstein College of Medicine

³Division of Respiratory and Sleep Medicine, Children's Hospital at Montefiore – Albert Einstein College of Medicine

Abstract

Objective—To determine if adenotonsillar hypertrophy is an isolated factor in pediatric obstructive sleep apnea (OSA) or if it is part of larger spectrum of cervical lymphoid hypertrophy.

Study Design—Prospective case control study.

Methods—A total of 70 screened patients (mean age 7.47 years) underwent polysomnography to confirm OSA and then underwent MRI of the upper airway. 76 matched controls (mean age 8.00 years) who already had an MRI underwent polysomnography. Volumetric analysis of lymphoid tissue volumes was carried out. Chi-square analysis and Student's t-test were used to compare demographic data and lymph node volumes between cohorts. Fisher's Exact test and Chi-square analysis were used to compare sleep data.

Results—Patients and controls demonstrated no significant difference in mean age (7.47 vs 8.00 yrs), weight (44.87 vs 38.71 kg), height (124.68 vs 127.65 cm), or body-mass index (23.63 vs 20.87 kg/m²). OSA patients demonstrated poorer sleep measures than controls ($p < 0.05$) in all polysomnography categories (sleep efficiency, apnea index, apnea-hypopnea index, baseline SpO₂, SpO₂ nadir, baseline ETCO₂, peak ETCO₂, and arousal awakening index). Children with OSA had higher lymphoid tissue volumes than controls in the retropharyngeal region (3316 vs 2403 mm³, $p < 0.001$) upper jugular region (22202 vs 16819 mm³, $p < 0.005$), and adenotonsillar region (18994 vs 12675 mm³, $p < 0.0001$).

Conclusions—Children with OSA have larger volumes of deep cervical lymph nodes and adenotonsillar tissue than controls. This finding suggests a new paradigm in the understanding of pediatric OSA and has ramifications for future research and clinical care.

Keywords

MRI; sleep; apnea; children; etiology

Correspondence: Sanjay R. Parikh, MD, FACS, Division of Pediatric Otolaryngology-Head and Neck Surgery, Seattle Children's Hospital, 4800 Sand Point Way NE, W-7729, Seattle WA 98105, Tel: 206 987 3468, Fax: 206 987 3925, sanjay.parikh@seattlechildrens.org.

Conflicts of Interests:

Parikh: Consultant, Olympus

INTRODUCTION

Over the last 50 years, there has been a significant evolution in the diagnosis and management of pediatric OSA.¹⁻³ With advancements in polysomnography, accurate means of diagnosing OSA in children has become possible.^{4,5} Moreover, the entity of OSA as a whole and its untoward physical and neurocognitive effects on children have been studied and documented.⁶

Authorities now appreciate the association between pediatric OSA and transient nocturnal hypoxia and poor quality sleep, both of which can negatively impact daytime alertness, school performance, behavior, and cardiovascular status.⁷ At its worst, pediatric OSA has been associated with cognitive delays, hypertension, and heart failure.^{8,9} Despite the recognition of these associations, the precise etiology of pediatric OSA still remains unclear.

OSA and Adenotonsillar Hypertrophy(ATH)

Pediatric OSA has been clearly associated with ATH. However, the complete understanding of pediatric OSA and its distinct relationship with ATH remains nebulous. Certain factors have been identified which contribute to ATH including genetic predisposition and exposure to infectious pathogens.^{10,11} But it remains unknown why children with similar tonsil and adenoid size display a wide variance in clinical sleep symptoms.¹² Furthermore, it is unclear why tonsillectomy and adenoidectomy does not cure all children with OSA. Some studies suggest that as many as 1/3 of children have persistent OSA despite adenotonsillectomy.¹³ Our specialty has not achieved a framework to predict the likelihood of adenotonsillectomy success for children with OSA. At best, post-operative clinical symptoms and/or polysomnography can quantify post-surgical success, but even polysomnography suffers from limited availability and excessive cost.

Tonsillectomy and adenoidectomy (T&A) has evolved into a first line therapy for children with documented and undocumented OSA.¹⁴ It is one of the most common operative procedures performed, but comes at the cost of significant postoperative pain, the risk of hemorrhage, and a high annual healthcare expenditure.¹⁵ In the last quarter of a century, the indication for T&A has moved from chronic pharyngitis to obstructive sleep disordered breathing, reflecting the greater understanding of pediatric OSA and greater tolerance of chronic pharyngitis.¹⁶

OSA and Magnetic Resonance Imaging(MRI)

Over the last 30 years, MRI has become a global diagnostic modality for the evaluation of human soft tissue. In the past decade, MRI has been used to evaluate the upper airway in patients with sleep apnea.^{16,17} Two types of imaging have evolved – static and dynamic. With static imaging, MRI sequences are obtained as a “snap-shot” to evaluate the upper airway in patients with OSA.^{18,19} In dynamic studies, MRI sequences are captured as “films” to examine active movement of the upper airway soft tissues to elucidate obstructive pathologies (often referred to as Cine-MRI).²⁰⁻²³ Aside from inherent equipment and support costs, limits of such studies include the required supine position, and in the case of children, the frequent need for sedation, which may not accurately mimic physiologic sleep.

OSA and Cervical Lymph Node Hypertrophy

Our review revealed no studies supporting the thesis that cervical lymph node hypertrophy is associated with pediatric OSA. There have been case reports demonstrating OSA in patients with other lymphatic disorders such as malformation or neoplasia.²⁴⁻²⁷ However, there are no clinical standards for the evaluation of cervical lymph nodes in the management of OSA.

OBJECTIVES/HYPOTHESIS

Evaluation of Lymphoid Tissue Volume in Children with OSA

To determine if deep cervical lymph nodes are enlarged in pediatric patients with OSA. Our hypothesis is that pediatric OSA is a multi-factorial disease with multi-level obstruction and that increased deep cervical lymph node volume contributes to this disorder.

Experimental Evaluation of MRI Analysis of Cervical Lymphoid Tissue Volume

There have been no studies demonstrating a feasible diagnostic modality to assess cervical lymph node volumes. Previous studies have demonstrated that Waldeyer's Ring lymphoid tissue volumes can be accurately assessed by MRI. This study's secondary objective is to determine if computer assisted three dimensional volumetric analysis of cervical MRI can accurately assess deep cervical lymph node volumes.

MATERIALS AND METHODS

Institutional Review Board (IRB) approvals were obtained at all involved sites.

Subjects

The subjects in the age range of 2 to 17 yrs, with polysomnography confirmed OSA, were recruited from pediatric sleep disorders centers at the Children's Hospital of Philadelphia between the periods of 1998 and 2004 and the Children's Hospital at Montefiore between 2008 and 2011. Informed consent was obtained from recruited subjects' parent(s) or guardian(s), and assent was obtained from children older than 7 years as per IRB protocol. Subjects were excluded if they had a history of tonsillectomy and/or adenoidectomy. Also, subjects with any significant co-morbid conditions contributing to OSA, such as: Trisomy 21, craniofacial anomalies, and cerebral palsy were also excluded from the study.

Controls

Children in the age range of 2 to 17 yrs, who underwent head and neck MRI for non-sleep related complaints at the Children's Hospital of Philadelphia between the periods of 1998 and 2004 and at Children's Hospital at Montefiore between 2008 and 2011 and were recruited as controls. Subjects were included when the indication for MRI had no bearing on upper airway structure and included conditions such as: headaches, trauma, seizure convulsion, etc. Informed consent was obtained from recruited subjects' parent(s) or guardian(s) and assent was obtained from children older than 7 years as per IRB protocol. All controls underwent polysomnography and those with OSA were excluded as well any controls with a history of tonsillectomy and/or adenoidectomy or any significant co morbid conditions contributing to OSA.²⁸

Controls were obtained from children who underwent head and neck MRI for non-sleep related complaints. All patients were clinically justified in undergoing MRI of the head and neck for other reasons (eg. headaches, trauma, seizures, etc). Informed consent was obtained from recruited subjects' parent(s) or guardian(s) as per IRB protocol. Patients were excluded if they had a history suspicious for sleep apnea based on questionnaire or a history of tonsillectomy and/or adenoidectomy.²⁸

Polysomnography

Both subjects and controls underwent overnight polysomnography using a computerized acquisition system (Somnostar, SensorMedics, Yorba Linda, CA or Xltek, Oakville, ON, Canada). Variables recorded were: sleep stage by scalp electrodes (F₄-M₁, C₄-M₁, O₂-M₁,

and F₃-M₂, C₃-M₂, O₁-M₂), muscle tone by EMG, thoracoabdominal movement by piezoelectric belts (Sleepmate, Midlothian, VA), inspired and expired end-tidal CO₂ tension (P_{ET}CO₂) by capnography (Capnogard 1265; Novametrix, Wallingford, CT), airflow by nasal pressure (Pro-Tech, Mukilteo, WA) and 3-pronged thermistor, (Nihon Kohden, Tokyo, Japan, arterial oxygen saturation (SpO₂, averaging time of 2 seconds) by pulse oximetry (Masimo, Irvine, CA), heart rate and ECG, and continuous infra-red video digital recording with audio.

Scoring of polysomnographic variables was performed as per the guidelines of the American Thoracic Society and published data in children. We defined OSA as cessation of airflow with absence of thoraco-abdominal movement. Hypopnea was defined as a 50% reduction in airflow and concurrent arousal or 3% drop in oxygen saturation.

MRI

MRI was performed with a 1.5 Tesla machine (Siemens Vision System, Iselin, NJ) with an anterior-posterior head coil. All patients and controls (below 7 years of age) received intravenous pentobarbital at a dose of 2 mg/kg. Up to two more doses at 2 mg/kg up to a maximum of 200 mg were given if sleep was not achieved. Once asleep, subjects were positioned supine with the head's Frankfort plane (tragus to orbital fissure) perpendicular to the table.

T1 and T2 axial images were obtained from the roof of the orbit to the level of the cricoid. T1 and T2 sagittal images were obtained from the midline bilaterally. T1 coronal images were obtained from the anterior nose to the posterior spinal cord. Specific sequence parameters were used for each patient in each plane:

1. T1 Axial – TR=650 msec, TE=14 msec, 192×256 matrix, 3 mm slices with 0 distance factor, 1 acq, FOV=20–24 cm, RECFOV 6/8
2. T2 Axial – TR=6000 msec, TE=90 msec, 110×256 matrix, 3 mm slices with 0 distance factor, 1 acq, FOV=20–24 cm, RECFOV 6/8
3. T1 Sagittal – TR=650 msec, TE=14 msec, 192×256 matrix, 3 mm slices with 0 distance factor, 1 acq, FOV=20–24 cm, RECFOV 8/8
4. T2 Sagittal – TR=6000 msec, TE=90 msec, 132×256 matrix, 3 mm slices with 0 distance factor, 1 acq, FOV=20–24 cm, RECFOV 8/8
5. T1 Coronal – TR=6000 msec, TE=97 msec, 150×202 matrix, 4 mm slices with 0 distance factor, 1 acq, FOV=20–24 cm, RECFOV 6/8

Lymphoid tissue definitions

Four specific regions of lymphoid tissue were delineated on MRI based on location and signal pattern diagnostic for lymphoid tissue. The four regions delineated were tonsil, adenoid, retropharyngeal nodes (defined as lymph nodes located between the internal carotid arteries from the skull base to the hyoid bone), and the upper jugular lymph nodes (defined as lymph nodes, located along the internal jugular vein from the skull base to the hyoid bone). Tonsil and adenoid volume was defined as the sum of tonsil and adenoid volumes. Total deep cervical lymph node volume was defined as the sum of the retropharyngeal and upper jugular lymph node volumes.

Three dimensional volumetric analysis

MRI scans were reviewed individually and DICOM (Digital Imaging and Communications in Medicine) images were extracted and downloaded into Amira® software (Mercury

Computer Systems, Visage Imaging Inc, Carlsbad, CA, Version 4.1.1). Deep cervical lymph node volumes was manually delineated on each two-dimensional DICOM image using semi-automated interactive image segmentation technique based on signal density characteristics. Volumetric analysis was then performed using the Amira[®] software.

Statistical Analysis

Comparisons of demographic data between subjects and controls were carried out using Student's t-test, except for gender ratio which was analyzed with Chi-square analysis. Data were presented with averages $\pm$ standard deviation. With regard to sleep data, independent samples were used to compare groups with normally distributed continuous variables, and Chi-square and Fisher's Exact tests were used for categorical variables. MRI lymphoid tissue volumes were compared between subjects and controls using Student's t-test and 95% confidence intervals were calculated and graphically plotted. Pearson's Correlation Coefficient was used to identify associations on scatter plotting of lymphoid tissue volumes and apnea-hypopnea indices.

RESULTS

Demographics

A total of 146 children were included for analysis, all of whom underwent polysomnography (PSG) and cervical MRI. Seventy were recruited from a sleep center by screening questionnaire and then underwent MRI and PSG. Seventy-six controls were recruited from a pool of patients who had already undergone cervical MRI for non-sleep related diagnoses. These controls then underwent PSG. A similar percentage of patients in both groups required sedation for MRI. No significant differences in age, gender, height, weight, and BMI were identified between OSA patients and controls (Table I).

Polysomnography

All recruited patients underwent polysomnography. Comparison of OSA patients' and controls' sleep efficiency, apnea index, apnea-hypopnea index, baseline SpO₂, and SpO₂ nadir, baseline ETCO₂, peak ETCO₂, and arousal awakening index showed statistical significance (Table II). The OSA group performed worse than controls in all measures. No statistical difference was found between the two groups' total sleep time.

Volumetric MRI Analysis

All OSA patients and controls underwent volumetric MRI analysis of cervical lymphoid tissue (Figure 1). Comparison of OSA patients' and controls' upper jugular, retropharyngeal, and total deep lymph node volumes showed statistical difference in all three accounts (Table III). OSA patients also demonstrated statistically larger adenotonsillar volume than controls (Table IV). Plotting of 95% confidence intervals for all cervical lymph node regions graphically demonstrated no overlap between OSA patients and controls (Figures 2, 3, & 4). Scatter plotting and Pearson's Correlation Coefficient(r) calculation between total deep cervical lymphoid volumes and age was carried out (Figure 5). This demonstrated a positive correlation between age and total deep cervical lymph node volumes in subjects ($r=0.74$) and controls ($r=0.67$). Similarly, scatter plotting and coefficient correlation between AHI and lymphoid tissue volumes in subjects was carried out (Figures 6 & 7). Positive correlations were identified in subjects between AHI and total deep cervical lymph node volume ($r=0.29$) and between AHI and total lymphoid tissue volume ($r=0.37$).

DISCUSSION

Comparison of lymphoid tissue volumes

No previous study has compared cervical lymph node volumes in patients with OSA versus controls. In this novel report, volumetric analysis was feasible given the reliable MRI signal of lymphoid tissue in the upper jugular and retropharyngeal areas. The limits of comparison of these areas include the inherent accuracy of MRI technology and the 3 mm slices used in our protocol. Although smaller slices may have resulted in more accurate volume analysis, the consistent imaging protocol in both cohorts nullifies the potential for bias or inconsistencies.

Feasibility of MRI analysis of cervical lymphoid tissue volumes

MRI has already been established as a useful modality for the evaluation of patients with sleep apnea.^{19,20} Studies have also demonstrated that MRI can reliably measure the volume of tonsil and lymphoid volumes.^{17,29} Using established signal intensities for lymphoid tissue, perimeters of lymphoid tissue can be identified. After highlighting these boundaries, volumetric analysis can be computed. We identified two areas where signal intensity and perimeters were in keeping with lymphoid tissue: the retropharyngeal region and upper jugular region. Tonsil and adenoid volumes could also be calculated based on established protocols.

Of note, one cannot assume that measured lymphoid tissue volumes in our study measure the entire complex cervical lymphatic system. Although we acknowledge the limits of these measurements, we applied the same measurement protocol to both the study and control cohorts. We believe that the recorded differences between the 2 cohorts' lymphoid tissue volume accurately reflects a legitimate difference. We believe the difference can be traced to an undefined systemic process within the OSA group.

Polysomnography

Polysomnography and scoring were performed as per the American Thoracic Guidelines. Although other polysomnography scoring methodologies exist, the consistent use of the identical system on both subjects and controls allowed for meaningful comparison. Every index of scoring showed statistical difference between OSA patients and controls yielding confidence in study design.

Theories of lymphoid hypertrophy and OSA

The exact role of ATH as it relates to the immune system is unknown. All classes of immunoglobulins have been identified in tonsillar lymphoid tissue.^{30–33} Hypertrophy of adenotonsillar tissue may occur as a response of exposure to infectious agents.^{34,35} Removal of the tonsils and adenoids have not demonstrated a negative effect on the immune system.^{36,37} Although there is familial concordance with adenotonsillar hypertrophy, an exact genetic signature has not been identified.^{38–40}

The precise relationship of ATH and OSA is also unknown. Most theories subscribe to laxity of the upper airway in deep phases of sleep with subsequent obstruction from adenotonsillar tissue.^{41,42} Additional factors such as obesity and tongue size have also been identified as contributing to upper airway obstruction.^{43–45}

ATH may be an isolated phenomenon of Waldeyer's ring or part of a larger lymphoproliferative disorder. We demonstrate that pediatric OSA patients with ATH also have hypertrophy of the entire cervical lymphoid system. This suggests the possibility that lymphoid hypertrophy outside of Waldeyer's ring contributes to pediatric OSA, and

challenges the concept that adenotonsillar hypertrophy is isolated to Waldeyer's ring in children with sleep apnea. This finding also suggests that OSA in children is a multifactorial disorder which includes obstructive contributions from cervical lymph node hypertrophy.

Our major finding in this work is that increased deep cervical lymph node size may reflect a broader respiratory perturbation in children. The cervical lymphatic system drains important craniofacial structures including: the nose, paranasal sinuses, middle ears, as well as other cranial and cervical lymphoid tissues such as those involved in Waldeyer's ring. Thus, such hypertrophy may reflect a broader disorder of lymphoid tissues due to inflammation and/or infections that may be recurrent or chronic.

One could argue that the cervical lymphoid hypertrophy outside Waldeyer's ring, while coexistent with ATH, makes no contribution to OSA. We have submitted no evidence to counter that claim. On the other hand, most clinicians who manage pediatric OSA understand that a significant number of children have ATH but minimal or no symptoms of sleep disordered breathing; it may be that neurologic factors alone account for this phenomenon, but anatomic factors such as cervical lymphoid hypertrophy may also be a contributor to some children's obstruction. The fact that obesity clearly causes an increase in OSA supports the notion that increased mass in the neck, as occurs with cervical lymph node hypertrophy, aggravates OSA. Future study should address the question of whether children with minimal response to tonsillectomy and adenoidectomy have an abnormal deep cervical lymph node volume.

Our finding of multi-level lymphoid hypertrophy in OSA patients also has therapeutic implications. Other studies have shown that anti-inflammatory pharmaceutical agents have a beneficial impact on patients with OSA but the mechanism of action is unknown.⁴⁶⁻⁴⁸ It is plausible that anti-inflammatories play a role in the downregulation of cervical and Waldeyer's lymphoid hypertrophy with secondary relief of upper airway obstruction. This hypothesis warrants further investigation as a potential new strategy for the management of children with OSA.

CONCLUSIONS

Three-dimensional volumetric analysis of MRI cervical lymph node volumes is a feasible study in children with OSA. Our initial evaluation of subjects with polysomnography proven sleep apnea and controls reveals statistically significant differences in the volumes of lymphoid tissue. Children with sleep apnea have greater volumes than controls of measured upper jugular, retropharyngeal, and total deep cervical lymph nodes. This revelation indicates that pediatric OSA is not only associated with isolated adenotonsillar hypertrophy but with hypertrophy of the entire cervical lymphoid system. This novel finding warrants further investigation to delineate potential diagnostic and treatment algorithms for deep cervical lymph node hypertrophy in the management of pediatric patients with OSA.

Acknowledgments

Support: NIH HD-53693, HL-HL-62408

References

1. Witmans M, Young R. Update on pediatric sleep-disordered breathing. *Pediatr Clin North Am*. 2011; 58:571-89. [PubMed: 21600343]

2. Halbower AC, Ishman SL, McGinley BM. Childhood obstructive sleep-disordered breathing: a clinical update and discussion of technological innovations and challenges. *Chest*. 2007; 132:2030–41. [PubMed: 18079240]
3. Gozal D, Kheirandish-Gozal L. New approaches to the diagnosis of sleep-disordered breathing in children. *Sleep Med*. 2010; 11:708–13. [PubMed: 20621557]
4. Wise MS, Nichols CD, Grigg-Damberger MM, et al. Executive summary of respiratory indications for polysomnography in children: an evidence-based review. *Sleep*. 2011; 34:389–98. [PubMed: 21359088]
5. Aurora RN, Zak RS, Karippot A, et al. Practice parameters for the respiratory indications for polysomnography in children. *Sleep*. 2011; 34:379–88. [PubMed: 21359087]
6. Beebe DW, Ris MD, Kramer ME, Long E, Amin R. The association between sleep disordered breathing, academic grades, and cognitive and behavioral functioning among overweight subjects during middle to late childhood. *Sleep*. 2010; 33:1447–56. [PubMed: 21102986]
7. Mitchell RB, Kelly J. Behavioral changes in children with mild sleep-disordered breathing or obstructive sleep apnea after adenotonsillectomy. *Laryngoscope*. 2007; 117:1685–8. [PubMed: 17667138]
8. Reeves G, Blaisdell C, Lapidus M, et al. Sleep architecture and behavioral abnormalities in children and adolescents. *Int J Adolesc Med Health*. 2010:22535–45.
9. Horne RS, Yang JS, Walter LM, et al. Elevated blood pressure during sleep and wake in children with sleep-disordered breathing. *Pediatrics*. 2011; 128:e85–92. [PubMed: 21708802]
10. Bixler EO, Vgontzas AN, Lin HM, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. *Sleep*. 2009; 32:731–6. [PubMed: 19544748]
11. Baugh RF, Archer SM, Mitchell RB, et al. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg*. 2011; 144:S1–30. [PubMed: 21493257]
12. Nolan J, Brietzke SE. Systematic review of pediatric tonsil size and polysomnogram-measured obstructive sleep apnea severity. *Otolaryngol Head Neck Surg*. 2011; 144:844–50. [PubMed: 21493309]
13. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med*. 2010; 182:676–83. [PubMed: 20448096]
14. Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2009; 140:800–8. [PubMed: 19467393]
15. Parker NP, Walner DL. Trends in the indications for pediatric tonsillectomy or adenotonsillectomy. *Int J Pediatr Otorhinolaryngol*. 2011; 75:282–5. [PubMed: 21168225]
16. Arens R, McDonough JM, Costantino AT, et al. Magnetic resonance imaging of the upper airway structure of children with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 2001; 164:698–703. [PubMed: 11520739]
17. Welch KC, Foster GD, Ritter CT, et al. A novel volumetric magnetic resonance imaging paradigm to study upper airway anatomy. *Sleep*. 2002; 25:532–42. [PubMed: 12150320]
18. Suto Y, Matsuda E, Inoue Y, Suzuki T, Ohta Y. Sleep apnea syndrome: comparison of MR imaging of the oropharynx with physiologic indexes. *Radiology*. 1996; 201:393–8. [PubMed: 8888230]
19. Ciscar MA, Juan G, Martínez V, et al. Magnetic resonance imaging of the pharynx in OSA patients and healthy subjects. *Eur Respir J*. 2001; 17:79–86. [PubMed: 11307760]
20. Donnelly LF, Surdulescu V, Chini BA, et al. Upper airway motion detected at cine MR imaging performed during sleep: comparison between young patients with and those without obstructive sleep apnea. *Radiology*. 2003; 227:239–45. [PubMed: 12616001]
21. Donnelly LF. Obstructive sleep apnea in pediatric patients: evaluation with cine MR sleep studies. *Radiology*. 2005; 236:768–78. [PubMed: 16014437]
22. Moon IJ, Han DH, Kim JW, et al. Sleep magnetic resonance imaging as a new diagnostic method in obstructive sleep apnea syndrome. *Laryngoscope*. 2010; 120:2546–54. [PubMed: 21108433]
23. Barrera JE. Sleep magnetic resonance imaging: dynamic characteristics of the airway during sleep in obstructive sleep apnea syndrome. *Laryngoscope*. 2011; 121:1327–35. [PubMed: 21557247]

24. Kahn A, Blum D, Hoffman A, Hamoir M, et al. Obstructive sleep apnea induced by a parapharyngeal cystic hygroma in an infant. *Sleep*. 1985; 8:363–6. [PubMed: 3880177]
25. Jasper RD, Goldberg MG, Zborowski RG. Lymphangioma and cystic hygroma. Correction of facial growth disharmony and obstructive sleep apnea. *Int J Oral Maxillofac Surg*. 1989; 18:152–4. [PubMed: 2503575]
26. Gomez-Merino E, Arriero JM, Chiner E, Signes-Costa J, Marco J. Obstructive sleep apnea syndrome as first manifestations of pharyngeal non-Hodgkin's lymphoma. *Respiration*. 2003; 70:107–9. [PubMed: 12584402]
27. Tsou YA, Cheng YK, Lin CD, Chang WC, Tsai MH. Small B cell lymphocytic lymphoma presenting as obstructive sleep apnea. *World J Surg Oncol*. 2004; 2:26. [PubMed: 15282026]
28. Brouillette R, hanson D, David R, et al. A diagnostic approach to suspected obstructive sleep apnea in children. *Journal of Pediatrics*. 1984; 105:10–14. [PubMed: 6737123]
29. Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. *Am J Respir Crit Care Med*. 2003; 168:522–30. [PubMed: 12746251]
30. Kuki K, Tabata T. Immunohistological studies on tonsils of recurrent tonsillitis and tonsils with focal infections. *Acta Otolaryngol Suppl*. 1988; 454:75–82. [PubMed: 3223270]
31. Agren K, Andersson U, Litton M, et al. The production of immunoregulatory cytokines is localized to the extra follicular area of human tonsils. *Acta Otolaryngol*. 1996; 116:477–85. [PubMed: 8790751]
32. Andersson J, Abrams J, Björk L, et al. Concomitant in vivo production of 19 different cytokines in human tonsils. *Immunology*. 1994; 83:16–24. [PubMed: 7821961]
33. van Laar JM, Melchers M, Teng YK, et al. Sustained secretion of immunoglobulin by long-lived human tonsil plasma cells. *Am J Pathol*. 2007; 171:917–27. [PubMed: 17690187]
34. Piacentini GL, Peroni DG, Blasi F, et al. Atypical bacteria in adenoids and tonsils of children requiring adenotonsillectomy. *Acta Otolaryngol*. 2010; 130:620–5. [PubMed: 19958241]
35. DeDio RM, Tom LW, McGowan KL, et al. Microbiology of the tonsils and adenoids in a pediatric population. *Arch Otolaryngol Head Neck Surg*. 1988; 114:763–5. [PubMed: 3382530]
36. Paradise JL, Bluestone CD, Bachman RZ, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med*. 1984; 310:674–83. [PubMed: 6700642]
37. Paradise JL, Bluestone CD, Colborn DK, et al. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. *Pediatrics*. 2002; 110:7–15. [PubMed: 12093941]
38. Friberg D, Sundquist J, Li X, Hemminki K, Sundquist K. Sibling risk of pediatric obstructive sleep apnea syndrome and adenotonsillar hypertrophy. *Sleep*. 2009; 32:1077–83. [PubMed: 19725259]
39. Capper R, Canter RJ. Is the incidence of tonsillectomy influenced by the family medical or social history? *Clin Otolaryngol Allied Sci*. 2001; 26:484–7. [PubMed: 11843928]
40. Bixler EO, Vgontzas AN, Lin HM, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. *Sleep*. 2009; 32:731–6. [PubMed: 19544748]
41. Rojewski TE, Schuller DE, Clark RW, Schmidt HS, Potts RE. Video endoscopic determination of the mechanism of obstruction in obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 1984; 92:127–31. [PubMed: 6425764]
42. Katz ES, D'Ambrosio CM. Pathophysiology of pediatric obstructive sleep apnea. *Proc Am Thorac Soc*. 2008; 5:253–62. [PubMed: 18250219]
43. Gozal D, Kheirandish-Gozal L. Obesity and excessive daytime sleepiness in prepubertal children with obstructive sleep apnea. *Pediatrics*. 2009; 123:13–8. [PubMed: 19117855]
44. Dayyat E, Kheirandish-Gozal L, Sans Capdevila O, Maarafeya MM, Gozal D. Obstructive sleep apnea in children: relative contributions of body mass index and adenotonsillar hypertrophy. *Chest*. 2009; 136:137–44. [PubMed: 19225059]
45. Wootten CT, Shott SR. Evolving therapies to treat retroglossal and base-of-tongue obstruction in pediatric obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2010; 136:983–7. [PubMed: 20956744]

46. Kuhle S, Urschitz MS. Anti-inflammatory medications for obstructive sleep apnea in children. *Cochrane Database Syst Rev*. 2011; 1:CD007074. [PubMed: 21249687]
47. Kheriandish-Gozal, L.; Serpero, LD.; Dayyat, E., et al. Corticosteroids suppress in vitro tonsillar proliferation in children with obstructive sleep apnea.
48. Goldbart AD, Tal A. Inflammation and sleep disordered breathing in children: a state-of-the-art review. *Pediatr Pulmonol*. 2008; 43:1151–60. [PubMed: 19009600]

Figure 1. MRI volumetric analysis of lymphoid tissue volumes in an OSA patient (green-upper jugular lymph nodes, orange-tonsil tissue, red-retropharyngeal lymph nodes, magenta-adenoid tissue). **A.** Three dimensional reconstruction of lymphoid tissue using Amira[®] software. **B.** Axial T2-weighted DICOM image with lymphoid tissue tracings. **C.** Coronal T2-weighted DICOM image with lymphoid tissue tracings. **D.** Sagittal T2-weighted DICOM image with lymphoid tissue tracings.

Figure 2. Comparison of retropharyngeal lymph node volumes in OSA patients and controls (95% confidence intervals).

Figure 3. Comparison of upper jugular lymph node volumes in OSA patients and controls (95% confidence intervals).

Figure 4. Comparison of total deep cervical lymph node volumes in OSA patients and controls (95% confidence intervals).

Figure 5.

Figure 5a & 5b. Scatter plots and coefficient correlation between total deep cervical lymph node volume and age with linear trends in OSA subjects (top) and controls (bottom).

Figure 6. Scatter plot and coefficient correlation between AHI and subjects total deep cervical node volume.

Figure 7.
Scatter plot and coefficient correlation between AHI and combined subject lymphoid tissue volumes(tonsils, adenoid, retropharyngeal lymph nodes and upper jugular lymph nodes)

Table I

Demographic comparison of OSA patients and controls(mean $\pm$ standard deviation).

	OSA Patients (n=70)	Controls (n=76)	P-value
Age (years)	7.47 $\pm$ 4.55	8.00 $\pm$ 3.61	p>0.05
Gender (male/female)	45/27	40/36	p>0.05
Height (cm)	124.68 $\pm$ 27.88	127.65 $\pm$ 22.03	p>0.05
Weight (Kg)	44.87 $\pm$ 39.10	38.71 $\pm$ 29.84	p>0.05
BMI (kg/m²)	23.63 $\pm$ 10.83	20.87 $\pm$ 7.86	p>0.05

Student's t-test was used for all data comparisons except for gender ratio where Chi-Square analysis was used.

Table II

Comparison of polysomnography between OSA patients and controls (mean $\pm$ standard deviation).

	OSA Patients (n=70)	Controls (n=76)	p-Value
Total sleep time (hr)	7.06 $\pm$ 1.22	7.27 $\pm$ 1.01	NS
Sleep efficiency (%)	84.97 $\pm$ 10.29	88.19 $\pm$ 6.58	< 0.05
Apnea Index	3.44 $\pm$ 4.81	0.10 $\pm$ 0.24	< 0.001
Apnea hypopnea index	11.39 $\pm$ 10.73	0.55 $\pm$ 0.82	< 0.001
Baseline SpO₂ (%)	96.75 $\pm$ 1.50	97.44 $\pm$ 1.35	< 0.01
SpO₂ nadir (%)	82.78 $\pm$ 8.75	92.47 $\pm$ 3.07	< 0.001
Baseline ETCO₂ (mm Hg)	40.05 $\pm$ 3.98	38.00 $\pm$ 5.50	< 0.05
Peak ETCO₂ (mmHg)	49.94 $\pm$ 6.26	43.60 $\pm$ 7.06	< 0.001
Arousal-wakening index	17.47 $\pm$ 9.37	10.99 $\pm$ 4.51	< 0.001

NS=No statistical difference.

Table III

Comparison of deep cervical lymph node volumes between OSA patients and controls (mean $\pm$ standard deviation)

	OSA Patients (n=70)	Controls (n=76)	P-Value
Upper Jugular nodes(mm³)	22202 $\pm$ 13805	16819 $\pm$ 8690	P<0.005
Retropharyngeal Nodes(mm³)	3316 $\pm$ 1874	2403 $\pm$ 1344	P<0.001
Total Deep Cervical Nodes (mm³)	25518 $\pm$ 14070	19223 $\pm$ 9074	P<0.002

Table IV

Comparison of tonsil and adenoid volumes between OSA patients and controls (mean $\pm$ standard deviation).

	OSA Patients (n=70)	Controls (n=76)	P-Value
Tonsils (mm³)	8244 $\pm$ 3686	5713 $\pm$ 1979	P < 0.0001
Adenoid (mm³)	10750 $\pm$ 4503	6961 $\pm$ 2580	P < 0.0001
Tonsils+ Adenoid (mm³)	18994 $\pm$ 6934	12675 $\pm$ 3753	P < 0.0001