CHEST

Original Research

SLEEP MEDICINE

Cysteinyl Leukotriene Receptors Are Expressed by Tonsillar T Cells of Children With Obstructive Sleep Apnea*

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Background: **Increased expression of cysteinyl leukotriene receptors (cysteinyl leukotriene receptor-1 [LT1-R]; cysteinyl leukotriene receptor-2 [LT2-R]) has been detected in adenotonsillar tissue from children with sleep-disordered breathing (SDB) compared to control subjects. LT1-R has been localized in myeloperoxidase-positive cells. This phenomenon possibly contributes to lymphoid tissue enlargement and may be related to systemic inflammation.**

Objective: **To characterize cells expressing LT1-R and LT2-R in tonsillar tissue and assess serum C-reactive protein (CRP) levels in children with and without SDB.**

Methods: **Immunohistochemistry with LT1-R and LT2-R antibodies was used to examine tonsils from children who had tonsillectomy (with or without adenoidectomy) for SDB and from control subjects operated for recurrent tonsillitis/otitis. All participants underwent preoperative polysomnography and measurement of morning serum CRP.**

Results: **Fifteen children with SDB (mean age ± SD, 6.4 ± 2.1 years; apnea-hypopnea index, 9.6 ± 5.6 episodes per hour) and 11 control subjects (age, 7.5 ± 2.8 years; apnea-hypopnea index, 7 ± 0.3/h) were examined. Immunoreactivity for LT1-R and LT2-R was detected in tonsillar extrafollicular areas of all subjects with SDB but not of control subjects. Cells expressing leukotriene receptors were CD3+ lymphocytes. Children with SDB and control subjects were similar regarding CRP levels: 0.11 ± 0.15 mg/dL vs 0.09 ± 0.15 mg/dL, respectively ($p > 0.05$).**

Conclusions: **Tonsils of children with SDB but not of control subjects have enhanced expression of cysteinyl leukotriene receptors in T lymphocytes without an associated increase in serum CRP concentration. Up-regulation of LT1-R and LT2-R could potentially promote tonsillar enlargement in children with obstructive sleep apnea.** ***(CHEST 2008; 134:324–331)***

Key words: adenoidal hypertrophy; adenotonsillectomy; montelukast; obstructive sleep-disordered breathing

Abbreviations: CRP = C-reactive protein; DAB = 3,3′-diaminobenzidine; LT1-R = cysteinyl leukotriene receptor-1; LT2-R = cysteinyl leukotriene receptor-2; SDB = sleep-disordered breathing

Increased upper airway resistance due to enlarged adenoids and tonsils plays a central role in the pathogenesis of obstructive sleep apnea in children.[1,2] Normally, soft tissues of the nasopharynx and oropharynx grow proportionally to the cranial skeleton.[3] However, children with obstructive sleep apnea have adenoids and tonsils that are disproportionate in size to the skeletal structures of the airway.[4]

It is unknown why in some children adenotonsillar tissue grows out of proportion to the upper airway lumen. Goldbart and colleagues[5,6] shed some light on this issue. They reported that subjects with obstructive sleep-disordered breathing (SDB) have increased expression of cysteinyl leukotriene receptors (cysteinyl leukotriene receptor-1 [LT1-R]; cysteinyl leukotriene receptor-2 [LT2-R]) and higher concentrations of leukotrienes $C_4/D_4/E_4$ in pharyngeal lymphoid tissue compared to children with recurrent tonsillitis.[5,6] Double-label immunohistochemistry for LT1-R and myeloperoxidase revealed that this receptor is located primarily in myeloper-

oxidase-positive cells.[6] It was proposed that increased expression of leukotriene receptors by myeloperoxidase-positive cells such as neutrophils and eosinophils may be related to adenotonsillar hypertrophy.[6] The above speculation is supported by the higher percentage of neutrophils found in sputum of children with obstructive sleep apnea relative to subjects without apnea.[7]

Presence of increased concentrations of cysteinyl leukotrienes in adenotonsillar tissue from children with SDB has been connected to the recurrent vibratory mechanical stress of snoring and possibly to ongoing, low-grade, systemic inflammation.[5,6,8] Nevertheless, systemic inflammation in subjects with SDB has not been consistently documented by all studies,[9,10] and this discrepancy between published investigations has been attributed to genetic and environmental factors.[8] Thus, the aims of the present study were the following: (1) to reproduce findings by Goldbart and colleagues[5,6] in a population with different genetic background and environmental influences compared to previously studied children; (2) characterize cells that express leukotriene receptors in tonsillar tissue of subjects with SDB; and (3) assess whether participants with SDB and high abundance of leukotriene receptors have also increased serum levels of C-reactive protein (CRP) relative to control subjects. In previously published studies,[5,6] cysteinyl leukotriene receptors have been localized in the extrafollicular areas of tonsils and adenoids by fluorescent microscopy. For this reason, we hypothesized that LT1-R and LT2-R are expressed by T lymphocytes, which consist the dominant cell population in the lymphoid tissue extrafollicular areas.

Materials and Methods

Participants

The study was approved by the Institutional Review Board; informed consent for participation was obtained from parents, and child assent from subjects > 7 years old. Consecutive children who underwent adenotonsillectomy for SDB over a period of 6 months and had preoperative polysomnography were eligible for recruitment. Indications for surgery were the following: (1) adenotonsillar hypertrophy (adenoids > 1 + and tonsils > 2 +)[11]; (2) symptoms of SDB > 3 nights per week; and (3) apnea-hypopnea index > 1 episode per hour. Children without SDB who had tonsillectomy (with or without adenoidectomy) for recurrent tonsillitis or otitis media and whose parents consented for performance of preoperative polysomnography were recruited as control subjects.

Exclusion criteria for both patients and control subjects were the following: (1) cardiovascular, neuromuscular, or genetic disorders; (2) symptoms or signs of acute or chronic inflammatory disorders; and (3) current use of nasal corticosteroids or cysteinyl leukotriene receptor inhibitors. In accordance with the published studies by Goldbart and colleagues,[5,6] subjects with recurrent tonsillitis or otitis media were not recruited in the control group if they had history of snoring. Presence of snoring with AHI < 1/h (primary snoring) is indicative of SDB, and its pathogenesis may be similar to that of obstructive sleep apnea syndrome.[12]

Clinical Evaluation, Polysomnography, and CRP Measurement

Preoperatively, information about symptoms of SDB and current and previous medical history were collected, and a detailed physical examination of all systems was performed. Symptoms of fever, cough, earache, sore throat, vomiting, diarrhea, dysouria, skin rash, or arthralgia were recorded. The parents were also specifically asked about a possible diagnosis of connective tissue disease in their child's medical history. Chronic nasal obstruction was the presence of congested nose for at least 3 months over the past 6 months or physician's diagnosis of chronic rhinitis. Weight and height were measured, and body mass index z score was calculated.[13] Size of tonsils and adenoids was graded from 0 to 4 + by direct inspection and transoral mirror visualization, respectively.[11]

Preoperative polysomnography for both patients and control subjects was completed overnight in the Sleep Disorders Laboratory. The Alice 4 computerized system (Healthdyne; Marietta, GA) was used, and the following parameters were recorded: EEG (C3/A2, C4/A1, O1/A2); right and left oculogram; submental and tibial electromyogram; body position; ECG; thoracic and abdominal wall motion (piezoelectric transducers); oronasal airflow (three-pronged thermistor); and oxygen saturation of hemoglobin. Arousals and sleep stages were assessed using standard criteria.[14,15] Obstructive apnea was defined as the presence of chest/abdominal wall motion in the absence of airflow for at least two breaths in duration.[16] Hypopnea was defined as a reduction in the airflow signal amplitude of at least 50% compared to baseline in the presence of chest/abdominal wall motion and associated with oxygen desaturation of hemoglobin ≥ 4% or with an arousal.[16]

Venipuncture was performed between 8:00 and 10:00 AM; serum was obtained from the blood sample and was stored at −70°C until assay. CRP levels were quantified by a high-sensitivity, immunonephelometric method with a lowest detection limit of 0.0175 mg/dL (N High Sensitivity CRP; Dade Behring; Marburg, Germany).

Immunohistochemistry

Immunoperoxidase staining was performed with antibodies directed against LT1-R (1:400) and LT2-R (1:1000) [Cayman Chemical; Ann Arbor, MI], CD3 (1:50), CD4 (1:25), CD8 (1:50), CD68 (1:50), and myeloperoxidase (1:50) [DAKO; Glostrup, Denmark]. Examination of tissue specimens with light micros-

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copy was completed by a single pathologist (M.G.I.) blinded to the initial diagnosis of each subject. Tonsillar tissues were fixed in buffered formalin 4%, processed routinely, and embedded in paraffin. Sections were cut at 3 μm using a microtome (RM2145; Leica Microsystems; Wetzlar, Germany) and dried overnight at 60°C. After deparaffinization in xylol, tissue sections were rehydrated in decreasing ethanol solutions and incubated in 0.3% hydrogen peroxide in methanol for 15 min to block endogenous peroxidase.

Antigen retrieval using 0.01 mol/L citrate buffer solution (pH 6) heated for 20 min in a microwave oven was performed prior to staining. After antigen retrieval, tissue sections were cooled and washed three times in phosphate-buffered saline solution. Subsequently, they were incubated overnight at 4°C with each antibody. After specimens were washed by phosphate-buffered saline solution, Envision fluid (polymer-peroxidase method) [EnVision + /HRP; DAKO] was added, followed by incubation for 30 min. Bound antibodies were visualized using 3,3′-diaminobenzidine (DAB) solution (DAKO). Finally, sections were counterstained with hematoxylin and mounted in Entellan medium (Merck; Darmstadt, Germany). Negative controls were prepared by omitting the primary antibody for LT1-R and LT2-R. Normal histology of tonsillar tissue is presented in Figure 1.

Since accurate colocalization of two antigens (*eg*, LT1-R and CD3) in a tissue with high cellularity such as tonsils may be difficult, double indirect immunofluorescence studies were performed in adjacent formalin-fixed, paraffin-embedded tissue sections utilizing the same antibodies against LT1-R (1:200), LT2-R (1:200), and CD3 (pan-T cell marker) [1:50]. Fluorescent anti-mouse and anti-rabbit secondary antibodies (1:500) [Invitrogen Corporation; Carlsbad, CA], a fluorescent microscope and a digital camera were used for detection of immunoreactivity.

Statistics

The two study groups were compared regarding subject characteristics, polysomnography findings, presence of leukotriene receptors, and serum CRP levels. Student *t* test was used for continuous variables and χ^2 test (Yates correction) for categorical characteristics.

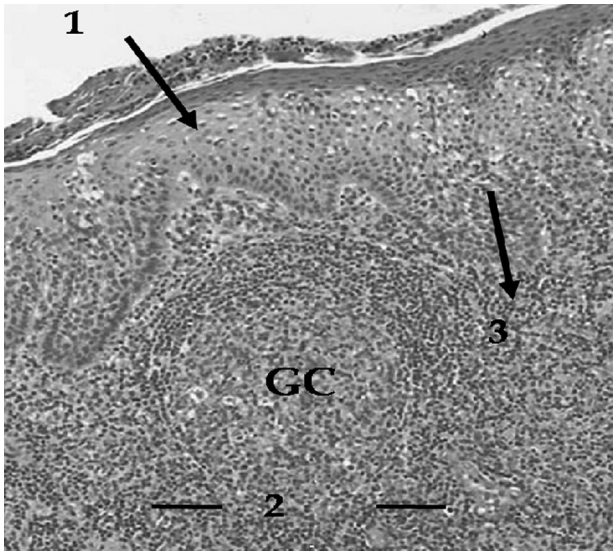

FIGURE 1. Normal histology of tonsillar tissue includes a surface epithelium of stratified squamous type (arrow 1) overlying the lamina propria. Tonsillar lymphoid tissue is composed of lymphoid follicles (2) with germinal centers (GC) and extrafollicular/paracortical areas (arrow 3). The lymphoid cells in the follicles are of B-cell lineage, whereas the extrafollicular/paracortical areas comprise mostly T lymphoid cells.

RESULTS

Subject Characteristics and Polysomnography Findings

Fifteen children who underwent adenotonsillectomy for obstructive SDB after preoperative polysomnography were recruited. All of them had snoring more frequently than 3 nights/week. During the same time period, 11 children without symptoms of SDB who had tonsillectomy (with or without adenoidectomy) for recurrent tonsillitis or otitis and polysomnography prior to surgery were also included in the study (control group).

Subject characteristics, results of preoperative polysomnography, and type of surgery are summarized in Tables 1, 2. Preoperative apnea-hypopnea index ranged from 1.4 to 21.8/h in patients and from 0.2 to 0.9/h in control subjects. The two study groups were similar regarding age at surgery, female-to-male ratio, body mass index z score, proportion of obese participants, tonsillar and adenoidal size, and type of surgery (adenotonsillectomy or tonsillectomy without adenoidectomy). Patients with SDB had more frequently history of chronic nasal obstruction compared to control subjects ($p = 0.04$).

Immunohistochemistry

SDB Group: LT1-R and LT2-R immunoreactivity was detected in tonsillar epithelial cells and in cells of the extrafollicular areas between the follicles of all children with SDB (Fig 2, *top left*, *A*, and *bottom left*, *C*). These cells were CD3 + T lymphocytes (Fig 3, *left*, *A*). Immunohistochemical analysis with CD4 and CD8 antibodies showed that T lymphocytes were predominantly CD4 + (Fig 3, *center*, *B*). Only a minority of them were CD8 + T lymphocytes (Fig 3, *right*, *C*). No immunostaining was identified in the lymphoid cells of germinal centers. However, a few cells within the germinal centers showed positive staining for LT1-R and LT2-R (Fig 2, *top left*, *A*, and *bottom left*, *C*). These cells were found to be CD68 + macrophages (not shown).

Control Group: Specimens from control subjects without SDB showed immunoexpression of LT1-R and LT2-R in epithelial cells (Fig 2, *top right*, *B*, and *bottom right*, *D*). Immunoreactivity in the tonsillar lymphoid tissue (extrafollicular areas or germinal centers) was not identified in any subjects of the control group (Fig 2, *top right*, *B*, and *bottom right*, *D*). A few cells within the germinal centers showed

Table 1—*Summary Statistics and Significance of Comparisons Regarding Preoperative Characteristics of Children Who Underwent Adenotonsillectomy for Obstructive SDB and Control Subjects Who Had Tonsillectomy (With or Without Adenoidectomy) for Other Indications

Variables	Subjects With SDB (n = 15)	Control Subjects (n = 11)	p Value
Age at surgery, yr	6.4 ± 2.1	7.5 ± 2.8	0.28
Female gender, %	5 (33.3)	4 (36.4)	1.00
Chronic nasal obstruction	13 (86.7)	5 (45.5)	0.04
BMI z score	0.8 ± 1.4	0.7 ± 1	0.8
Obese	6 (40)	2 (18.2)	0.39
Tonsil size			
≤ 2 +	1 (6.7)	0 (0)	1.00
> 2 +	14 (93.3)	11 (100)	
Adenoid size			
1 +	0 (0)	18.2 (2)	0.17
≥ 2 +	15 (100)	81.8 (9)	
Type of surgery			
Adenotonsillectomy	15 (100)	10 (90.9)	0.42
Tonsillectomy only	0 (0)	1 (9.1)	

*Data are presented as mean ± SD or No. (%). BMI = body mass index.

immunoreactivity for LT1-R and LT2-R. These cells were CD68 + macrophages (not shown).

Results of immunohistochemistry for both study groups are summarized in Table 3 (p = 0.001 for comparisons between study groups regarding presence of LT1-R and LT2-R in the tonsillar extrafollicular areas). Polymorphonuclear neutrophils (myeloperoxidase-producing cells) expressing LT1-R and LT2-R were identified in tonsillar tissue of children with SDB and control subjects within small vessels between the mantles of adjacent follicles. A few of them were also scattered in the germinal centers (data not shown).

Colocalization of LT1-R or LT2-R With CD3 by Immunofluorescent Microscopy: Double indirect immunofluorescence studies in tonsillar tissue from children with SDB confirmed that LT1-R or LT2-R were expressed by CD3 + lymphocytes located mainly in the tonsillar extrafollicular areas. Representative lymphoid tissue section stained against LT1-R and CD3 is shown in Figure 4.

Serum CRP levels

Subjects with SDB and control subjects were similar regarding preoperative mean (± SD) CRP levels: 0.11 ± 0.15 mg/dL vs 0.09 ± 0.15 mg/dL, respectively (p = 0.83).

Discussion

Our results are for the most part, in agreement with findings of two previous reports[5,6] on LT1-R and LT2-R expression in adenoidal and tonsillar tissue from children with SDB. Both published investigations and the current report have identified immunostaining for LT1-R and LT2-R in tonsillar extrafollicular areas of children with sleep apnea but not of control subjects. Additionally in this study, use of immunohistochemistry and double indirect immunofluorescence allowed us to define the type of cells expressing LT1-R and LT2-R in patients with SDB. Cells with cysteinyl leukotriene receptors are T lymphocytes (predominantly CD4 +), the most prevalent cellular population between B-cell

Table 2—*Summary Statistics and Significance of Comparisons Regarding Polysomnography Indices in Children With Obstructive SDB and in Control Subjects Who Had Tonsillectomy (With or Without Adenoidectomy) for Other Indications

Variables	Subjects With SDB (n = 15)	Control Subjects (n = 11)	p Value
AHI, episodes/h	9.6 ± 5.6	0.7 ± 0.3	<0.001
Spo_2 nadir, %	82.7 ± 6.6	92 ± 1.2	<0.001
Oxygen desaturation of hemoglobin (> 4%) index, episodes/h	9.1 ± 5.8	0.63 ± 0.26	<0.001
Percentage of sleep time with Spo_2 < 95%	6.4 ± 7.7	0.35 ± 0.23	0.021
Respiratory arousal index, episodes/h	4 ± 3	0.49 ± 0.21	0.001

*Data are presented as mean ± SD. Spo_2 = oxygen saturation of hemoglobin by pulse oximetry.

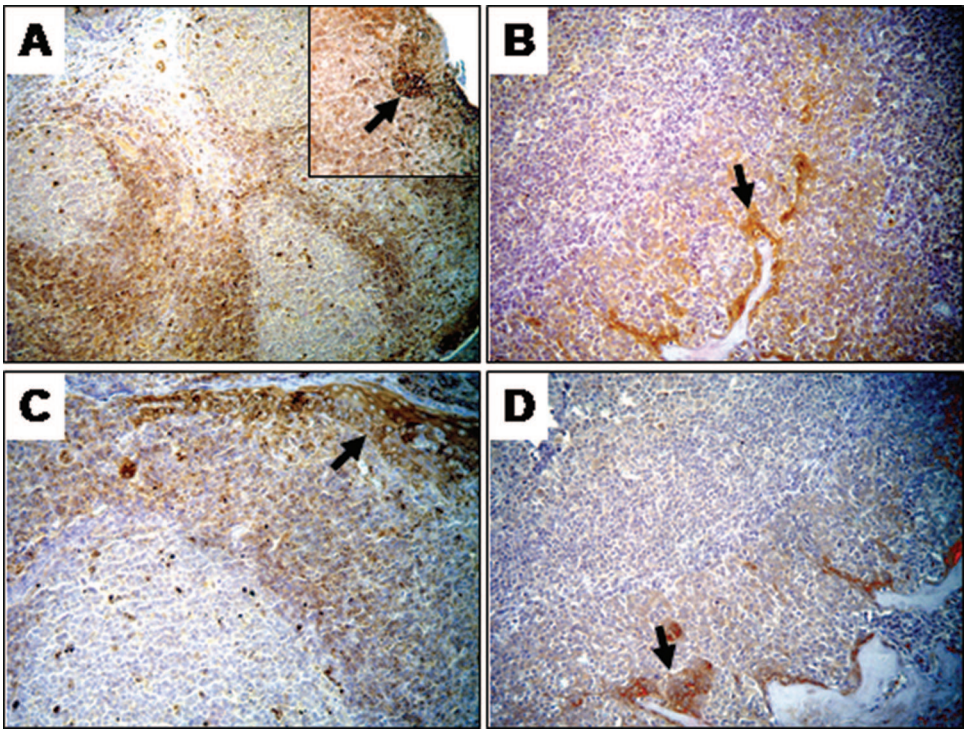

FIGURE 2. Immunohistochemistry (immunoperoxidase, DAB chromogen) for cysteinyl leukotriene receptors LT1-R (*top panels*) and LT2-R (*bottom panels*) in children with sleep-disordered breathing (*top left*, *A*, and *bottom left*, *C*) and control subjects (*top right*, *B*, and *bottom right*, *D*). There is enhanced immunoreactivity (brown) for LT1-R and LT2-R in epithelial layers of both study groups (black arrows) and in the extrafollicular areas of participants with sleep-disordered breathing (*top left*, *A*, and *top right*, *C*). A few cells with positive staining for LT1-R and LT2-R are seen within the germinal centers of the sleep-disordered breathing group (*top left*, *A*, and *bottom left*, *C*). These cells were found to be CD68 + macrophages (not shown).

follicles. Although patients and control subjects differed in the expression of leukotriene receptors, they were similar regarding serum CRP levels. This finding does not support the concept that expression of LT1-R and LT2-R is related to low-grade systemic inflammation.[6]

Patency of the upper airway during sleep is the result of complex interactions between the following: (1) upper airway resistance determined by anatomic factors; (2) upper airway neuromotor tone modifying airway resistance; and (3) negative intraluminal pressure generated mainly by the inspiratory diaphragmatic contraction.[17] Enlarged tonsils and adenoids increase resistance to airflow in children with obstructive sleep apnea.[4] Amelioration of obstructive SDB in young age after treatment with nasal corticosteroids or montelukast supports the concept of an immunologic or inflammatory component in the pathogenesis of pediatric sleep apnea.[6,18–22] But how does airway inflammation affect resistance to airflow?

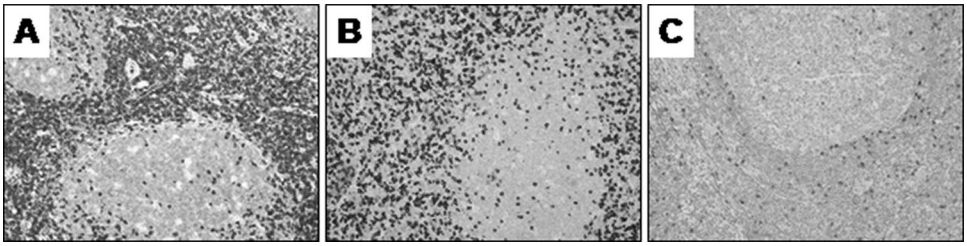

FIGURE 3. Cells between lymphoid follicles expressing LT1-R and LT2-R in children with SDB are CD3 + T lymphocytes (*left*, *A*). Immunohistochemical analysis with CD4 and CD8 antibodies showed that T lymphocytes were predominantly CD4 + (*center*, *B*), and only a minority of them were CD8 + (*right*, *C*) [immunoperoxidase, DAB chromogen].

Table 3—*Summary of Immunohistochemistry Results for LT1-R and LT2-R Expression in Tonsils of Patients With Obstructive SDB and of Control Subjects*

Variables	Epithelial Layers	Extrafollicular Areas	Macrophages in Germinal Centers
LT1-R and LT2-R in patients with SDB	Yes	Yes	Yes
LT1-R and LT2-R in control subjects	Yes	No	Yes

Adults with obstructive sleep apnea have nasal and pharyngeal mucosa inflammation.[23–25] Moreover, habitual snoring in children is associated with chronic nasal obstruction,[26] which may indicate the presence of mucosal inflammation contributing to increased nasal resistance. Of note, participants of the current study with SDB had significantly higher frequency of chronic nasal obstruction relative to control subjects. Elevated cysteinyl leukotriene concentrations in the exhaled breath condensate of children with habitual snoring and apnea-hypopnea index > 5/h most likely reflect nasal and pharyngeal inflammation, the latter possibly promoting upper airway collapsibility.[27,28] Finally, reduction of adenoidal size in children with mild SDB (apnea hypopnea index < 5/h) following a 16-week course of oral montelukast implies that LT1-R and LT2-R contribute to pharyngeal lymphoid tissue enlargement.[6]

The current study adds one more piece to the pathogenetic puzzle of tonsillar enlargement in children with obstructive SDB: LT1-R and LT2-R within the tonsillar extrafollicular areas are expressed by T lymphocytes. T lymphocytes are also the dominant inflammatory cells in the pharyngeal mucosa of adults with obstructive sleep apnea.[23,29] It is known that sleep apneic children have high prevalence of allergic sensitization and that atopy determined by skin prick testing is associated with habitual snoring at 1 year of age.[30,31] Exposure of peripheral blood T and B lymphocytes to interleukin-4, a cytokine characterizing allergic inflammation, induces expression of LT1-R and LT2-R.[32] Therefore, atopic predisposition of children with

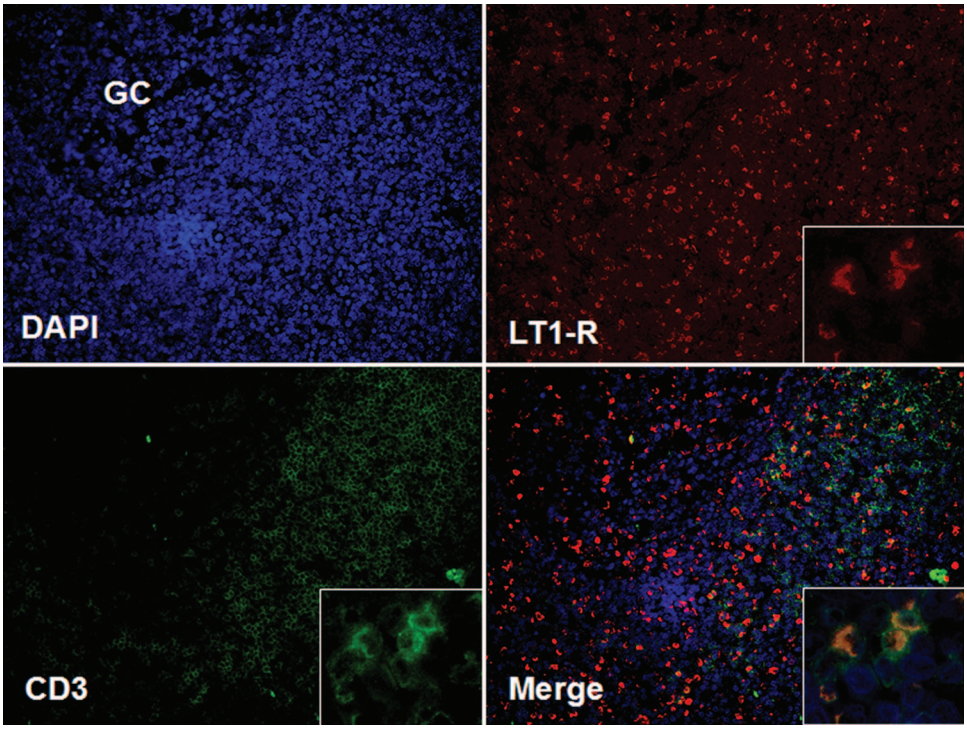

FIGURE 4. *Top left*: Fluorescent DAPI staining of one tonsillar germinal center (GC) and the adjacent extrafollicular area of a patient who had adenotonsillectomy for obstructive SDB. *Top right* and *bottom left* (same tissue section): Immunoreactivity for LT1-R (red color) and CD3 (green color) is mainly located in the tonsillar extrafollicular area. Merging the three pictures (*bottom right*) reveals that LT1-R is expressed by a subset of CD3 + tonsillar lymphocytes (orange/yellow color). Insets show high-power view of T lymphocytes coexpressing CD3 and LT1-R (original magnification of nail panels × 200 and insets × 1,000). Similar results were obtained for LT2-R and CD3 in the same tonsil (not shown).

SDB and subsequent sensitization to allergens can conceivably increase cysteinyl leukotriene receptors in tonsillar T lymphocytes and ultimately lead to pharyngeal tissue enlargement and obstructive sleep apnea. Indeed, higher prevalence of chronic nasal obstruction in the group of participants with SDB compared to control subjects of this report may reflect underlying allergy. However, allergic sensitization was not assessed by either radioallergosorbent testing or skin-prick testing and this is a limitation of the present investigation.

In a previous report,[6] LT1-R was found to be expressed by myeloperoxidase-positive cells. In this study, immunohistochemistry in tonsillar tissue of children with SDB or control subjects revealed that myeloperoxidase-producing cells were polymorphonuclear neutrophils seen primarily in small vessels between the mantles of adjacent follicles. Histopathologic experience indicates that in general extensive tonsillar infiltration by polymorphonuclear neutrophils is unusual except for cases of suppurative tonsillitis.

Goldbart and colleagues[6] have reported increased concentrations of cysteinyl leukotrienes in tonsils and adenoids of children with SDB. The effects of leukotrienes in adenotonsillar tissue have not been explored. Nevertheless, when mice lacking leukotriene C_4 synthase undergoes ovalbumin sensitization and then challenge, the number of parabronchial lymph node cells and their ability to produce T-helper type 2 cell cytokines are reduced.[33] We suggest that the beneficial effect of montelukast in children with obstructive sleep apnea is due to decreased proliferative activity and increased apoptotic death of activated T lymphocytes after binding of the medication on leukotriene 1 receptor.[34]

Alternatively, it has been suggested that the vibratory mechanical stress of snoring and associated local inflammation may contribute to upregulation of the cysteinyl leukotriene receptors in the pharyngeal lymphoid tissue.[6] Evaluation of the musculature in surgical specimens from the soft palate and tonsillar pillars of sleep apneic adults has shown denervation changes and infiltration by CD4+ T cells as opposed to infiltration by both CD4+ and CD8+ T cells that has been recognized in the pharyngeal mucosa.[23] Of interest, immunohistochemistry of uvula mucosa from adults with sleep apnea has also revealed increased numbers of leukocytes in the lamina propria that are mainly T lymphocytes.[29] In other words, inflammation in the pharyngeal mucosa of adults with SDB has a different pattern compared to inflammation within the upper airway musculature that may be the result of the mechanical trauma of snoring and potentially contributes to increased pharyngeal collapsibility.[28]

Systemic low-grade inflammation related to nocturnal intermittent hypoxemia and oxidative stress can play a role in the pathophysiology of pediatric SDB,[35] and it has been suggested that it initiates or maintains upper airway inflammatory processes.[6] Some pediatric studies[36,37] have reported a correlation between CRP and SDB, but others[9,10] did not reproduce this finding. The former investigations[36,37] were performed in children living in the United States, whereas the latter[9,10] were performed in Greek and Australian children. Discrepancies in results between studies may be due to genetic and environmental differences in study participants.[8]

In the current report, we provide evidence for more frequent expression of LT1-R and LT2-R in tonsils of Greek children with SDB compared to control subjects, a finding in agreement with results of the study by Goldbart and colleagues[5,6] in US children. Nevertheless, patients and control subjects did not differ in serum CRP levels, suggesting that systemic inflammation is probably unrelated to the upregulation of cysteinyl leukotriene receptors occurring in the pharyngeal lymphoid tissue. Measurement of other inflammatory markers such as serum interleukin 1, interleukin 8, and tumor necrosis factor-α is necessary to confirm this statement. Finally, a recent hypothesis[38] suggests that early exposure to respiratory syncytial virus modifies proliferation of adenotonsillar tissue through up-regulation of nerve growth factor and neurokinin 1 receptor-dependent pathways.

In conclusion, expression of cysteinyl leukotriene receptors in tonsillar tissue of children with SDB was confirmed in a group of subjects with different genetic background and environmental influences compared to participants of previously published pediatric studies. LT1-R and LT2-R are expressed preferentially by T lymphocytes within the tonsillar extrafollicular areas of children with sleep apnea and their presence is probably not related to systemic inflammation. Although published data indicate that upper airway inflammation in adults is most likely a consequence of intermittent upper airway obstruction, we propose that expression of LT1-R and LT2-R in tonsillar tissue during childhood may be the result of allergic sensitization and could promote SDB by causing pharyngeal lymphoid tissue enlargement. This speculative statement needs further testing.

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