Editorial

What Does the Microbiome in the Tonsil Tell Us?

Sung-Woo Cho ⓘD · Seung Koo Yang ⓘD

Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seongnam, Korea

Tonsil and adenoid hypertrophy is the main cause of pediatric obstructive sleep apnea, which can cause growth retardation [1], daytime sleepiness, emotional problems, and poor school performance in children [2]. The high incidence of pediatric obstructive sleep apnea—to which tonsil and adenoid hypertrophy contributes—together with the corresponding performance of tonsillectomy and adenoidectomy [3] causes a significant socioeconomic burden. As tonsil and adenoid tissue are lymphoid organs that are directly in contact with the environment in the oral cavity and upper airway, numerous studies have explored microbial interactions in the context of tonsil and adenoid disease.

Associations between tonsillar hypertrophy and microbial interactions have been demonstrated in several studies. The bacterial load from tonsil tissue samples was found to be directly proportional to tonsil size [4]. Beta-defensin-1, an endogenous bactericidal protein in tonsil tissue, is usually present in the basal lamina. Beta-defensin-1 is a cationic peptide that penetrates the negatively charged bacterial wall. The expression of human beta-defensin-1 is related to the 5' untranslated region (UTR), and some patients with tonsillar hypertrophy have a rare haplotype of this 5' UTR [5]. Another study demonstrated an association of adenovirus with tonsillar hypertrophy. The expression of major capsid protein VP1, a viral protein, in the tonsillar tissue was significantly higher in samples from patients with tonsillar hypertrophy than in control tissue or tissue samples from patients with recurrent tonsillitis [6]. Group A Streptococcus, known to be an important pathogen related to acute and recurrent tonsillitis, produces exotoxin streptolysin O, which interacts with toll-like receptor (TLR) 4 on the cell surface of tonsil mononuclear cells, which then induces the production of cysteinyl leukotrienes (CysLTs). CysLTs then interact with LT1-R, which is expressed by T and B cells, and stimulates the proliferation of tonsillar helper T cells and plasma B cells, leading to hyperplasia [7].

Most previous knowledge of the microbiology of adenotonsillar disease has been derived from culture-based studies, which reflect only a small fraction of the entire microbiome. Recent polymerase chain reaction amplification of 16S rRNA genes, a cornerstone in contemporary microbiome analyses, has been employed in several studies of the tonsil and adenoid. In the pediatric population, the microbial composition in patients with tonsillar hyperplasia is known to be different from that in patients with recurrent tonsillitis [8]. Jensen et al. [9] reported that the microbiota of the tonsillar crypt varies according to age and health status. *Haemophilus influenzae*, *Neisseria* species, and *Streptococcus pneumoniae* were exclusively detected in children, whereas *Prevotella*, *Actinomyces*, *Parvimonas*, *Veillonella*, and *Treponema* were significantly more abundant in adults. In children with tonsillar hyperplasia, the following genera predominated in the tonsillar crypts: *Streptococcus* (21.5%), *Neisseria* (13.5%), *Prevotella* (12.0%), *Haemophilus* (10.2%), *Porphyromonas* (9.0%), *Gemella* (8.6%), and *Fusobacterium* species (6.4%). The species composition of *Neisseria* differed between samples from children with tonsillar hyperplasia and samples from children with recurrent tonsillitis. *Fusobacterium necrophorum*, *Streptococcus intermedius*, and *Prevotella melaninogenica/histicola* were associated with recurrent tonsillitis in adults. The phylogenetic community structures were different, suggesting significant differences between the tonsillar crypt microbiota in healthy adults and adults with recurrent tonsillitis, and somewhat different community structures in children with recurrent tonsillitis and children with tonsillar hyperplasia [9].

Compared to recurrent tonsillitis, tissues from patients with tonsillar hypertrophy are known to express higher levels of interleukin (IL)-37 [10]. In addition, tissues from patients with tonsillar hypertrophy also have shown increased expression of innate immune mediators, including interferon-alpha, mitochondrial antiviral-signaling protein, NLR family pyrin domain containing 3 (NLRP3), and TLR 4 and TLR7 [11]. In contrast, tissues from patients with recurrent tonsillitis exhibited reduced antibody responses and aberrant CD 4 (+) T cells with increased PD-1 (+) CD 4 (+) T cells, suggesting T-cell exhaustion due to chronic infection [12,13]. These studies demonstrate that the degree and type of inflammation may differ between tonsillar hypertrophy and chronic tonsillitis.

The existence of a distinctive microbiome profile in tissues from children with recurrent tonsillitis and tonsillar hypertrophy may suggest that the different inflammatory profiles can partially be explained by differences in microbiome composition. In the current issue of *Clinical and Experimental Otorhinolaryngology*, Kim and Min [14] analyzed the adenotonsillar tissue microbiome from pediatric patients with snoring and inflammatory mediators, including IL-8 and heat shock protein 27, from lavage samples and suggested a possible association between them.

Taken together, modern 16s rRNA sequencing can be used to identify the diverse microbial community in the tonsil. The regional microbial composition interacts with the host mucosal immune system and is associated with the characteristic phenotype of tonsillar disease. Whether the microbial composition of the tonsil is affected by the severity of obstructive sleep apnea in pediatric patients remains to be determined. Detailed research regarding these interactions would enhance the current understanding of the pathogenesis of tonsillar disease.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Sung-Woo Cho   https://orcid.org/0000-0003-0827-4471
Seung Koo Yang   https://orcid.org/0000-0003-3519-7395

AUTHOR CONTRIBUTIONS

Conceptualization: SWC. Data curation: SWC. Formal analysis: SWC. Funding acquisition: SWC. Methodology: SWC. Project administration: SWC. Visualization: SWC. Writing–original draft: SWC. Writing–review & editing: SKY.

REFERENCES

1. Yilmaz MD, Hosal AS, Oguz H, Yordam N, Kaya S. The effects of tonsillectomy and adenoidectomy on serum IGF-I and IGFBP3 levels in children. Laryngoscope. 2002 May;112(5):922-5.
2. Liu J, Liu X, Ji X, Wang Y, Zhou G, Chen X. Sleep disordered breathing symptoms and daytime sleepiness are associated with emotional problems and poor school performance in children. Psychiatry Res. 2016 Aug;242:218-25.
3. Hall MJ, Schwartzman A, Zhang J, Liu X. Ambulatory surgery data from hospitals and ambulatory surgery centers: United States, 2010. Natl Health Stat Report. 2017 Feb;(102):1-15.
4. Brodsky L, Moore L, Stanievich JF, Ogra PL. The immunology of tonsils in children: the effect of bacterial load on the presence of B- and T-cell subsets. Laryngoscope. 1988 Jan;98(1):93-8.
5. Zupin L, Celsi F, Bresciani M, Orzan E, Grasso DL, Crovella S. Human beta defensin-1 is involved in the susceptibility to adeno-tonsillar hypertrophy. Int J Pediatr Otorhinolaryngol. 2018 Apr;107:135-9.
6. Proenca-Modena JL, de Souza Cardoso R, Criado MF, Milanez GP, de Souza WM, Parise PL, et al. Human adenovirus replication and persistence in hypertrophic adenoids and palatine tonsils in children. J Med Virol. 2019 Jul;91(7):1250-62.
7. Viciani E, Montagnani F, Tavarini S, Tordini G, Maccari S, Morandi M, et al. Paediatric obstructive sleep apnoea syndrome (OSAS) is associated with tonsil colonisation by Streptococcus pyogenes. Sci Rep. 2016 Feb;6:20609.
8. Watanabe H, Goto S, Mori H, Higashi K, Hosomichi K, Aizawa N, et al. Comprehensive microbiome analysis of tonsillar crypts in IgA nephropathy. Nephrol Dial Transplant. 2017 Dec;32(12):2072-9.
9. Jensen A, Fago-Olsen H, Sorensen CH, Kilian M. Molecular mapping to species level of the tonsillar crypt microbiota associated with health and recurrent tonsillitis. PLoS One. 2013;8(2):e56418.
10. Mikola E, Elenius V, Saarinen M, Palomares O, Waris M, Turunen R, et al. Tonsillar cytokine expression between patients with tonsillar hypertrophy and recurrent tonsillitis. Clin Transl Allergy. 2018 May;8:22.
11. Huang Q, Hua H, Li W, Chen X, Cheng L. Simple hypertrophic tonsils have more active innate immune and inflammatory responses than hypertrophic tonsils with recurrent inflammation in children. J Otolaryngol Head Neck Surg. 2020 Jun;49(1):35.
12. Dan JM, Havenar-Daughton C, Kendric K, Al-Kolla R, Kaushik K, Rosales SL, et al. Recurrent group A Streptococcus tonsillitis is an immunosusceptibility disease involving antibody deficiency and aberrant TFH cells. Sci Transl Med. 2019 Feb;11(478):eaau3776.
13. Geißler K, Markwart R, Requardt RP, Weigel C, Schubert K, Scherag A, et al. Functional characterization of T-cells from palatine tonsils in patients with chronic tonsillitis. PLoS One. 2017 Sep;12(9):e0183214.
14. Kim KS, Min HJ. Correlations between the adenotonsillar microbiome and clinical characteristics of pediatric patients with snoring. Clin Exp Otorhinolaryngol. 2021 Aug;14(3):295-302.