Role of Adenoids and Adenoiditis in Children With Allergy and Otitis Media

Gian Luigi Marseglia, MD, Dimitri Poddighe, MD, Davide Caimmi, MD, Alessia Marseglia, MD, Silvia Caimmi, MD, Giorgio Ciprandi, MD, Catherine Klersy, MD, Fabio Pagella, MD, and Anna Maria Castellazzi, PhD

Corresponding author
Gian Luigi Marseglia, MD
Department of Pediatric Sciences, Foundation IRCCS Policlinico San Matteo—University of Pavia, P.le Golgi, 2-27100, Pavia, Italy.
E-mail: gl.marseglia@smatteo.pv.it

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Adenoids and/or tonsil inflammation with concomitant obstructive hypertrophy is one of the oldest and most common pediatric problems. Adenoids are a component of Waldeyer's ring and because of their anatomic position can be relevant in the pathogenesis of otitis media when they are inflamed and/or enlarged. Adenoid pads can create mechanical eustachian tube obstruction. Therefore, in some cases, adenoidectomy may have a role in the clinical management of otitis media with effusion. However, eustachian tube dysfunction related to the adenoids may also have an allergy-related functional component. Allergic inflammation has been described for middle ear effusion, and some studies have reported that mast cells increase and allergic mediators release in adenoids as well. Nasal endoscopy has a key role in confirming a diagnosis of adenoid hypertrophy and/or adenoiditis and in detecting an association between adenoid inflammation/infection and otitis media with effusion, especially during infancy and early childhood.

Introduction

The mucosal-associated lymphoid tissues of the upper airways are arranged in a circular disposition around the wall of the throat and thus are known as Waldeyer's ring. It consists of the adenoid or nasopharyngeal tonsil (behind the nasal cavities), the palatine tonsils (at the entrance of the oropharynx), and the lingual tonsils (in the glossoepiglottic space). These structures represent the primary defense against microbes entering through the respiratory tract. Waldeyer's ring is therefore a critical site for antigen presentation and for the overall development of a local immune response.

Bacteria frequently attach to the adenoid surface, but because it is covered by a viscous secretion, it can bind microorganisms and play a local immunologic role. Adenoids are organized in deep crypts outlined with a specialized lympho-epithelium designed for entrapping foreign material: indeed, the lympho-epithelium consists not only of epithelial cells but also of lymphocytes, macrophages, and dendritic cells. On a deeper level, the lymphoid tissue is characterized by the presence of follicular germinal centers and interfollicular areas, which are populated predominantly by T lymphocytes [1].

The localization and function of effector T cells is crucial to the generation of an effective immune response. In particular, $CD8^+$ T lymphocytes can mobilize two main mechanisms: cytolysis and production of cytokines, chemokines, and microbicidal molecules. In cases in which the production of interferon-γ is reduced, patients show an increased susceptibility to infectious viral diseases—which often precede upper respiratory tract infections—with a possible consequential increase in replication of pathogenic bacteria in the adenoidal tissue [2].

The lymphoid tissue is not apparent in early infancy, as it gradually becomes hypertrophic and hyperplasic, acquiring its greatest relative mass between 2 and 5 years of age; during puberty, it undergoes an involution until, eventually, it is greatly reduced in older adults. Thus, Waldeyer's ring develops mostly during childhood, when the oronasopharyngeal space is not yet fully developed. These considerations may explain why inflammation of tonsils and adenoids, with subsequent obstructive hypertrophy, is one of the oldest and most common pediatric problems [3].

Palatine tonsils, along with adenoids, have been suggested as a potential site of bacteria colonization. Pathogenic bacteria are also often isolated from the nasopharynx of healthy children as transient or regular constituents of the nasopharyngeal flora. These isolates can include *Neisseria* spp, *Streptococcus pyo-*

genes, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Actinomyces*, *Bacteroides*, *Peptostreptococcus*, and *Fusobacterium* spp.

Mucins covering nasopharyngeal mucosa may function as receptor molecules for bacteria. Such an interaction is described mainly for *H. influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. This binding is important to prevent the adhesion to the epithelial surface and the penetration into the mucosa and therefore to avoid a potential infection, which also should be fought by local specific immunity, particularly secretory IgA [4•,5].

In normal conditions, the active interaction between innate and adaptive immunity and with nonspecific mechanical factors may be able to contribute to the prevention of microorganism invasion. This interaction is partially caused by Toll-like receptors that may nonetheless be reduced in children with recurrent respiratory infections or who have been exposed to passive smoke. This would then suggest a crucial immunologic function for Toll-like receptors in upper airway diseases [6]. Moreover, in children exposed to passive smoke, a reduction in T-helper type 1 adenoidal lymphocytes (interferon-γ–$CD8^+$) can be detected and becomes even more evident in patients presenting with recurrent respiratory infections [7].

The impairment of immunologic and nonimmunologic (eg, mucins) defenses and/or an increase in bacterial resistance may lead to colonization/persistence of pathogenic bacteria on the mucosa and even on adenoid/tonsil surfaces. As for the latter aspect, we now know that many bacteria in vivo tend to exist in complex aggregates attached to surfaces known as biofilms; such a spatial organization provides protection for bacteria against host immunologic defenses and antibiotics and therefore predisposes individuals to the development of upper airway infections [8,9•].

The clinical features of adenoiditis are very similar to those of acute rhinosinusitis, especially in younger children; in some cases, the symptoms of these conditions may overlap, and there is no pathognomonic sign. In these cases, nasal endoscopy can better visualize the adenoid area. In fact, nasal endoscopy is considered the gold standard, as it allows investigators to visualize adenoids and rhinopharynx structures directly (in general) and in a minimally invasive manner, even in young patients [10].

Adenoids, Adenoiditis, and Otitis Media

The concept that adenoids can worsen middle ear disease has been proposed for decades, especially when there is not only a simple hypertrophy but also an ongoing inflammatory/infectious process, namely adenoiditis. Moreover, some bacteria (which are actually those commonly detected in children's upper respiratory tract infections) can organize in biofilms on the adenoidal tissue, supporting the hypothesis that adenoids can also serve as bacterial reservoirs [6,11,12].

Thus, adenoiditis may lead to chronic or recurrent upper airway infections, including middle ear disease. Bacteria can persist on the adenoid surface by forming biofilms, and an inflammatory/purulent process can be present during asymptomatic periods. However, bacterial proliferation within the adenoids and tonsils is difficult to assess quantitatively by microbial culture.

Moreover, adenoid pads can create anatomic eustachian tube (ET) obstruction when they are enlarged and/or inflamed. Indeed, the most recurrent cause of ET dysfunction in children is related to obstruction caused by adenoid hypertrophy; this condition, which is characterized by marked proliferation of lymphoreticular tissue, is particularly common in children 4 to 6 years of age.

As for these patients, since 1980, adenoidectomy and sometimes adenotonsillectomy have been thought to have a role in the management of some patients with otitis media with effusion (OME) or recurrent acute otitis media. Current American Academy of Pediatrics clinical practice guidelines consider a child with middle ear disease a candidate for adenoidectomy only in a few cases, unless a distinct indication exists; however, adenoidectomy (with or without myringotomy) is recommended when children who have had a tympanostomy tube implanted have an OME relapse following tube extrusion [13,14]. The potential effectiveness of this surgery for otitis media in children older than 3 or 4 years of age is recognized; on the contrary, in younger patients, adenoidectomy does not seem to be beneficial [11,15,16].

Surgery may actually be considered for children presenting with recurrent rhinosinusitis and otitis. Furthermore, adenoids removed from children with chronic rhinosinusitis show more than 90% of the mucosal surface covered with biofilms, compared with 1.9% in children with simple obstructive sleep apnea [9•]. Microorganisms that are more often detected inside these bacterial biofilms include *S. aureus*, *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* (Stoodley and Nistico, unpublished data). The presence of biofilms suggests long-term colonization, which was also supported by their demonstration in surgical specimens removed from patients with refractory upper airway infections [4•,6,8].

Adenoids, Adenoiditis, and Allergy

Enlarged adenoids may contribute to ET dysfunction, causing mechanical obstruction. The obstruction may be related to several factors (eg, anatomic, physiologic, and inflammatory factors). However, in general, the recurrence of adenoid inflammation/infection is secondary to adenoid hypertrophy due to lymphoid tissue hyperplasia. Adenoids may cause ET dysfunction by promoting inflammatory changes in their proximity and even in the middle ear through the release of chemical mediators, as postulated in the "adenoid mediator release" theory. In fact, it seems as if adenoids may represent a potential site of allergic inflammation, which may provide a further

link between allergy and middle ear disease. In 1985, Collins and colleagues [17] found that the total amount of histamine in adenoids from patients with bilateral middle ear effusion at the time of adenotonsillectomy was significantly higher than in children without this clinical finding, although they did not investigate the allergic basis of the release of this mediator.

The possibility that an allergic process occurs in adenoids arose in 1970, as IgE-coated mast cells and plasma cells were demonstrated in this tissue. In 1984, Loesel [18] proposed the term *allergic adenoiditis* to indicate the presence of cell infiltrate characterized by numerous IgE-positive mast cells in the adenoid tissue.

Several studies have underlined the role played by the interaction of viral infections and allergic rhinitis in the pathogenesis of OME [19]. Adenoiditis also has been considered a potential site of allergic inflammation, which may establish a further link between allergy, especially allergic rhinitis, and OME.

The Link Between Adenoids, Adenoiditis, Otitis Media, and Allergy

That patients with OME present with an increased number of adenoid mast cells has been reported in a few more recent studies. Thus, an immediate-type hypersensitivity reaction can trigger their degranulation with release of histamine and other allergic mediators [20,21•]. A study that evaluated mast cell ultrastructure in the adenoids of children with and without OME could not demonstrate an increased rate of degranulation in the former group [22].

Other studies investigated immunologic aspects of adenoids in patients suffering from OME beyond specific allergy-related cells. No gross differences—regarding lymphoid and nonlymphoid elements—were found between adenoids from children with OME and those of patients with upper respiratory infections or adenoid hyperplasia without OME. In particular, the CD4:CD8 ratio of T lymphocytes and the proportions of major B-cell subsets were similar in the different patient groups [23,24].

On the contrary, Kiroglu and colleagues [25], using several techniques (light microscopy, immunocytochemistry, and electron microscopy), described an increased number of lymphocytes, mast cells, macrophages, dendritic cells, and M cells in adenoid tissue from patients with OME that seemed to be related to the presence of infectious foci. These data raise the issue of whether the handling of pathogens in adenoids of patients with OME is somehow impaired. Namely, there may be functional differences rather than differences in cell architecture.

Van Nieuwkerk et al. [26] first addressed the features of antigen-presenting cells of adenoids: they observed that only patients with OME showed dendritic cells in the epithelium and subepithelial layers. More recently, $CD1a^+$ cells, namely Langerhans cells, were reported in significantly greater numbers in the interfollicular area of adenoids from allergic patients [27]. These findings seem to suggest that there can be differences in antigen-presenting cells from the adenoids of patients with OME and with atopy that might affect allergic sensitization and immune response against microbes. Furthermore, Papatziamos and colleagues [28] described other immunophenotypical features of adenoids of atopic children: higher values of the $CD4^+/CD45RO^+$:$CD8^+/CD45RO^+$ T-cell ratio; increased numbers of IgE^+ and $Fc\varepsilon RI^+$ cells; and the presence of IgE^+ plasma cells, which are supposed to be derived from local differentiation.

Eventually, further insights on adenoids' pathological aspects and their relationship with allergy and otitis media have been gained by performing nasal endoscopy in children as well. This procedure allowed investigators to visualize adenoids and rhinopharynx structures directly in a minimally invasive manner. Cassano and colleagues [11] could not find a correlation between allergic rhinitis and adenoid hypertrophy, whereas a previous study reported the opposite conclusions, also indicating sensitization to mold allergen as a risk factor for adenoid hypertrophy in children with allergic rhinitis [16,29].

Our group performed a series of nasal endoscopy–based studies on a large pediatric population (287 consecutive children) suffering from persistent nasal obstruction symptoms. The first observations confirm the effectiveness of this procedure in diagnosing rhinosinusitis and adenoiditis. Clinical evaluation cannot distinguish appropriately between different patterns of nasal obstruction. In our cohort, with a clinical picture suggestive of rhinosinusitis, more than 90% were confirmed to be affected, but association with adenoiditis was found in almost 20% of cases; in addition, 7% of patients showed isolated adenoiditis. Adenoiditis— isolated or associated with rhinosinusitis—was more common in younger children (2–5 years of age, 33%; 6–10 years of age, 24%) and showed a progressive reduction in prevalence in older age groups (11–15 years of age, 13%), whereas the overall prevalence of rhinosinusitis remained consistent throughout different ages. Thus, adenoid inflammation seems to be a problem mainly among younger children, possibly because they are more vulnerable to recurrent respiratory infections [30].

Moreover, we assessed the association of allergy and specific endoscopic patterns in the same pediatric population. We also found that OME frequency seems to vary according to the endoscopic pattern, especially in younger age classes. Indeed, among those 2 to 5 years of age, OME showed a prevalence of 50%, 17%, and 42% in children with adenoiditis, rhinosinusitis, or both, respectively ($P < 0.001$); similarly, among 6- to 11-year-olds, the prevalence was 62%, 8%, and 58%, respectively ($P < 0.001$). In patients older than 11 years of age, there was no similar trend. These epidemiologic and clinical data seem to suggest a role for adenoid disease in the development of OME. Concerning the link between allergy and OME, the latter was diagnosed in 24% of allergic children and 15% of nonallergic children ($P < 0.05$), with frequencies

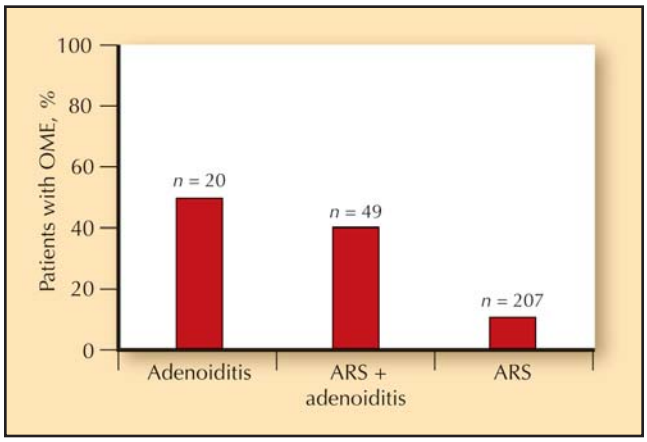

Figure 1. Breakdown of the population evaluated in the study by Marseglia et al. [31••]. The total number of patients presenting with otitis media with effusion (OME) was 53: 11% (n = 23) of those with acute rhinosinusitis (ARS), 50% (n = 10) of those with adenoiditis, and 40% (n = 20) of those with ARS and adenoiditis.

greater in the youngest children in both groups (43% vs 20%; $P < 0.05$) but still significantly different. In a multivariate analysis, allergic rhinitis ($P = 0.01$), an endoscopic pattern of adenoiditis ($P < 0.001$), and younger age ($P < 0.05$) were shown to be independently associated with a diagnosis of OME [31••]. The practical overall results of this study are well represented in Figure 1 [31••].

Future prospective studies could aim to further evaluate this association, considering also whether and how atopy and its clinical manifestations affect adenoid response, although a previous study from our group of a pediatric population of asthmatic children could not describe significant association between atopic condition and the endoscopic finding of rhinosinusitis and/or adenoiditis [29].

Conclusions

When a child presents with recurrent episodes of otitis media or with symptoms indicating a possible inflammation/infection of the adenoids, a complete medical evaluation should be conducted. Clinicians should carefully collect a detailed history of the child, investigate the allergic status of the patient, and perform a nasal endoscopy to reach a more precise diagnosis and to obtain microbiologic findings. Moreover, the abundance of purulent foci despite clinically undetectable infections underlines the need to perform such an examination in this group of patients.

Our understanding of the complex interplay among adenoiditis, allergy, and otitis media remains elusive. Further studies are needed to increase our knowledge on reciprocal and specific influences among all these factors. The finding that bacteria organize in vivo in biofilms provides an important element to explain their persistence on upper airway epithelial surfaces and also on mucosa-associated lymphoid tissue (eg, adenoids), which then have been proposed to serve as bacterial reservoirs. However, other noninfectious factors, mainly all that can be included in the category of ET dysfunction, seem to be relevant as well. Adenoid enlargement has been long recognized as the most common cause of ET dysfunction in children, who represent a predisposed population for anatomic reasons partially related to facial bone growth processes. In addition to the infectious pathology, adenoid size and function may be affected by other immunologic processes, such as allergy. Our specific knowledge is still very limited, and further studies are needed to provide new insights, but adenoids may be a potential site of allergic inflammation that can affect ET function through the release of chemical mediators. These observations can provide a further mechanism linking adenoids, allergy, and otitis media, although epidemiologic data are still quite controversial.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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