Nasal Polyps and Lower Respiratory Tract Relationship

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Core Messages

- Nasal polyps (NP) are most prevalent in asthma with aspirin hypersensitivity.
- Genetic factors are implicated in neutrophilic NP diagnosed in cystic fibrosis and ciliary disorders.
- Appropriate treatment of NP may result in the improvement of asthma control.
- NP in asthmatics are more frequently resistant to therapy.

13.1 Introduction

According to recent European guidelines, chronic rhinosinusitis (CRS) with nasal polyps (NP) and CRS without NP are nowadays considered two distinct entities with different inflammatory mechanisms [20]. Prior studies focusing on link between NP and lower respiratory tract frequently did not differentiate between patients with CRS with or without NP [3, 20]. In this chapter, only papers including subjects with NP will be discussed. Most studies addressed link between NP and bronchial asthma, whereas considerably much less is known about relationship between NP and lower airways in cystic fibrosis (CF), ciliary disorders, or immunodeficiencies.

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13.2 Prevalence of Nasal Polyps in Diseases of Lower Respiratory Tract

Reporting subjective nasal symptoms, without the use of nasal endoscopy or sinus computed tomography (CT), may bias epidemiological data on NP incidence in diseases of lower airways. NP affect about 2–4% of general population, 5% atopic asthmatics, and 13% of nonatopic athmatics [20, 30, 56]. The course of NP in asthmatics is usually more severe. In a tertiary care institution, asthmatics had significantly higher prevalence of NP (47 vs. 22%), olfactory dysfunction (26 vs. 6%), and nasal congestion (85 vs. 60%) than non-asthmatics [57]. They required significantly more revision sinus procedures overall (mean: 2.9 vs. 1.5) [57]. The most severe form of asthma, aspirin-induced asthma (AIA) is characterized by the highest prevalence of NP (36–60%) [62, 63].

On the other hand, in patients with NP, asthma can be found in 26% of cases, whereas episodes of wheezing are reported in up to 42% [30]. In about 70% of asthmatics, NP are diagnosed before asthma [20]. Gender seems to predict incidence of NP in asthma. Females with NP are 1.6 times more likely to be asthmatic [12]. AIA is also more prevalent in women in their thirties [62, 63]. Genetic factors are possibly implicated in NP origin. Children of patients with AIA and NP more commonly develop NP [40].

Much less epidemiologic data are published in other types of NP. NP diagnosed in children or showing

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neutrophilic infiltrates should raise suspicion of CF or ciliary disorders. The prevalence of NP in CF reaches 20%, whereas in Kartagener syndrome, a congenital ciliary dyskinesia, it is 30% [22].

NP in middle-aged females may indicate aspirin hypersensitivity, whereas in children – CF, ciliary disorders, or immunodeficiencies.

13.3 Link Between Nasal Polyps and Lower Airways

As more data emerge, it becomes obvious that the link between CRS with NP and lower airways includes several mechanisms. Importantly, NP impair basic functions of nasal mucosa: defending against infections and conditioning the air before entering lower airways. Viral and bacterial infections are common causes of asthma exacerbations [10]. The bronchial hyperresponsiveness (BNR) observed in patients with CRS and NP has been formerly explained by the activation of pharyngobronchial reflexes [20]. However, microaspiration of postnasal drip from sinuses into bronchi is irrelevant in conscious subjects [10, 20].

The concept with the best supporting evidence involves systemic propagation of inflammation from nasal to the bronchial mucosa by mediators and inflammatory cells stimulating bone marrow ("systemic cross-talk") [3, 10, 13, 20]. This systemic inflammation in respiratory tract results in a spectrum of manifestations – NP in upper airway and asthma, CF, or bronchiectases in lower airways.

The key mechanism in NP and lower airway disorders is systemic inflammation.

13.4 Inflammatory Mechanisms of NP in Diseases Other than Bronchial Asthma

The origin of NP in CF is linked to an impaired function of the chloride channels, resulting in an increase in mucus viscosity [1]. Almost all patients have severe involvement of sinuses [22]. Higher scores at initial sinus CT were risk factors for revision sinus surgery in CF [6]. Patients with CF suffer from recurrent infections in the respiratory tract, and their lung function has an obstructive or mixed pattern due to bronchiectases and lung fibrosis [22]. Interestingly, NP in patients with CF may indicate a higher frequency of chronic colonization of *P. aeruginosa* in the lower respiratory tract [23]. It was found that respiratory comorbidities in CF were asthma alone (28%) and aspirin hypersensitivity (5%) [6].

NP in CF are noneosinophilic. Unlike as in eosinophilic NP in asthmatics, no measurable levels of IL-5 in the nasal lavage in CF could be found [23]. Distinct cytokine pattern results from recurrent infections. In nasal lavage fluid in patients with CF and NP lysozyme and IL-8 concentrations were increased in comparison with the healthy control group [23]. The mainstays of CF treatment are lavage with saline solution, intranasal corticosteroids, antibiotics, and functional sinus endoscopic surgery.

The origin of CRS and NP in primary ciliary dyskinesia has been linked to an altered function or structure of the ciliated cells, which leads to a poor clearing of mucus [11, 22]. In lungs, purulent bronchial infections and bronchiectases are hallmarks of this disease [11]. A sinus CT scan usually demonstrates invasion of ethmoidal and maxillary sinuses, together with hypoplasia of the frontal sinus [22]. Therapy consists of respiratory physiotherapy with postural drainage, antibiotics for respiratory infections, and sinus surgery in resistant NP.

13.5 Inflammatory Mechanisms in NP and Bronchial Asthma

Eosinophilic NP are nowadays considered the T-helper-2 cytokine-mediated disease, with a high production of key regulatory cytokines such as IL-5 and IL-4 and formation of immunoglobulin E [3, 20]. This is in contrast to CRS without NP characterized by T-helper-1 cytokine pattern [20]. The importance of type 2 T-helper responses in the pathogenesis of asthma is well recognized [28]. IL-5 and eotaxin induce infiltrates of eosinophils in nasal and bronchial mucosa by increasing eosinophil chemotaxis, migration, activation, and prolonged survival [3, 20]. Activation of eosinophils, basophils, and T cells leads to a further release of mediators, e.g., potent proinflammatory agents such as cysteinyl leukotrienes (cys-Lts), which sustain chronic inflammation. The stimulation of the bone marrow leads to further recruitment of cells and

mediators into the lower respiratory tract. Eosinophil progenitors may migrate to the airways [61]. The highest concentrations of IL-5 were found in polyps in nonallergic asthma and aspirin hypersensitivity [31].

13.6 The Role of Cysteinyl Leukotrienes in Nasal Polyps and Bronchial Asthma

cys-LTs are potent proinflammatory mediators that contribute to pathophysiologic features of CRS, NP, and asthma as they increase microvascular permeability and mucus secretion, impair mucociliary clearance, induce long-lasting bronchospasm, and recruit eosinophils into the nasal mucosa [48].

The levels of cys-Lts appear to correlate with the extent of NP or bronchial asthma severity. Nasal mucosa was demonstrated to be an important source of urinary cys-Lts in AIA [41]. Also in patients with aspirin-tolerant asthma (ATA), similarly to those with AIA, urinary hyperleukotrienuria was associated with a more severe asthma and CRS with NP, as well as with hypereosinophilia and anosmia [24].

AIA, representing the most severe form of CRS with NP and bronchial asthma, is characterized by much higher levels of LTs as compared to ATA or healthy controls [62, 63]. High urinary leukotriene E_4 (LTE_4) may be a marker of NP. AIA with CRS and NP had the highest levels of urinary LTE_4 as compared to AIA with isolated CRS, mild atopic asthma, and normal controls [41]. Moreover, the rate of recurrences of AIA with NP in postoperative period was significantly higher in those with lower prostaglandin E2 (PGE2) or higher leukotriene C4 (LTC4) concentrations in nasal mucosa [29].

However, only eosinophilic NP are rich in leukotrienes. The cys-LTs concentrations within noneosinophilic NP were similar to those in control tissue [59]. In the same study, the presence of cys-LTs in eosinophilic CRS was linked with increased expression of LTC_4 synthase mRNA [59].

Treatment of CRS and NP may result in significant drop in cys-Lts global burden and possibly contribute to better postoperative asthma control. There were significant decreases in the urinary LTE_4 concentrations after the sinus surgery in both the AIA and ATA groups [24].

13.7 The Role of Microorganisms in Nasal Polyps and Bronchial Asthma

Enterotoxins of *Staphylococcus aureus* have been implicated in the pathophysiology of eosinophilic NP as they may considerably enhance T-helper-2 cytokine pattern typical for NP [4]. Specific IgE antibodies to enterotoxins A or B were demonstrated in 50–90% of patients with NP and their presence was related to a more pronounced eosinophilic inflammation and higher concentrations of ECP, IL-5, and eotaxin [4]. The role of nasal *S. aureus* in pathogenesis of severe asthma was suggested [4].

Fungal colonization in patients with NP may also precipitate Th 2 responses, and thus, perpetuate chronic inflammation in respiratory tract [50]. Eosinophilic mucin rhinosinusitis, devoid of fungal hyphae, had a significantly higher association with asthma, AIA, and an increased incidence of IgG1 deficiency [19].

Nevertheless, it is not clear whether *S. aureus* or fungal colonization is a primary or rather secondary phenomenon, due to imbalance in local defense mechanisms in advanced CRS with NP.

13.8 Effect of Nasal Polyps on Bronchial Hyperreactivity

Although a large number of studies proved the link between allergic or nonallergic rhinitis and BHR, there is still limited evidence of such relationship for NP [10, 13].

BHR can be demonstrated in 35% of patients with NP without asthma [52]. Lack of bronchial symptoms does not rule out a possibility of inflammation in lower airways. Asymptomatic BHR was associated with infiltrates of eosinophilis and lymphocytes in bronchial biopsies, similarly to asthmatics [18, 33]. An increased number of IL-5 protein(+) cells in bronchial biopsies in patients with NP and asymptomatic BHR as compared to patients with NP alone was demonstrated [35]. In patients with NP and BHR, an increased expression of IL-9 mRNA in bronchial biopsies, inversely correlating with the airway responsiveness to methacholine and positively with IL-5 mRNA expression or eosinophil infiltration, was found [64].

BHR in NP may be a risk factor of resistance to pharmacotherapy and a need for subsequent sinus

surgery. A therapeutic protocol consisting of short-term oral prednisolone and intranasal beclomethasone on a daily basis (for 3 years) proved successful in 93.4% of patients with isolated NP, in 82.2% with BHR, and only in 60% with BHR and AIA [8]. Significantly more patients with BHR or AIA required sinus surgery than those without BHR [8]. A prospective study demonstrated an increase of BHR and a decrease of FEV_1 over 12 months in patients with NP not responding to intranasal corticosteroids who underwent intranasal ethmoidectomy, whereas no change was observed in the group of responders [32]. Long-term observation of NP patients confirmed steady, irreversible decrease in FEV_1 over a period of 4 years [34].

It is likely that sinus surgery may result in disappearance of BHR and possibly interferes with potential asthma development in some patients with NP [27].

13.9 Effect of Sinus Surgery on Clinical and Therapeutic Outcomes of Bronchial Asthma

Sinus surgery for NP may influence the course of bronchial asthma, which is an additional proof of the close relationship between upper and lower respiratory tract. Today, the most appropriate way of surgical approach to extensive CRS and NP is endoscopic sinus surgery (ESS), whereas simple polypectomy should be avoided, especially in AIA [20, 63]. A recent systematic review showed that symptomatic improvement following FESS in patients with NP ranged from 78 to 88% as compared with 43–84% for comparative sinus procedures [16].

Most studies show that sinus surgery in asthmatics results in better asthma control, improvement of lung function tests, decrease in BHR, and reduction of doses of steroids [2, 7, 8, 17, 20, 36, 43]. Fifty asthmatics who failed to improvement following aggressive pharmacotherapy for CRS were observed for 12 months following ESS [17]. The authors found that 20% asthmatic patients could use less corticosteroids, whereas 28% bronchodilator inhalers [17]. In those patients the number of hospitalizations for asthma also dropped significantly [17].

Usually the most dramatic improvement of asthma occurs in the first year after sinus surgery [36, 51, 55]. However, in a study assessing long-term effect of ESS about 70% of patients who responded to standardized surveys reported further improvement in their asthma beyond the first postoperative year [36]. Sinus surgery may reduce costs of asthma control. In a questionnaire-based study, ESS in asthmatics resulted in a 75% reduction in the number of hospitalizations and 81% reduction in acute care visits within the year after the surgery (Nishioka 1994). However, there were also some studies indicating deterioration of asthma following sinus surgery [20].

On the other hand, the presence of asthma, or even more importantly AIA, may adversely affect outcomes of sinus surgery. In 119 adult patients with CRS, pre and postoperative quality of life parameters were negatively affected by incidence of AIA, depression, and female sex [58]. Moreover, endoscopy scores following sinus surgery were significantly worse in patients with asthma, aspirin hypersensitivity, prior sinus surgery, and NP [58].

Even well-performed ESS does not prevent relapses of NP in asthmatics and in some cases must be repeated [67]. Within a 3-year follow-up following sinus surgery impaired sense of smell returned again in patients with asthma or AIA [67]. AIA is well known for high frequency of NP relapses and the effect of sinus surgery on lung function in AIA seems more controversial [62, 63]. Patients with AIA undergoing sinus surgery did not experience a statistical improvement in postoperative FEV_1 and nasal symptoms, as did those with ATA within at least 12 months of follow-up [5]. However, another study demonstrated a significant improvement in postoperative lung function tests [43].

ESS is currently considered the most effective therapy in massive NP. In asthma, sinus surgery results in better asthma control, improvement of lung function, decrease in BHR, and reduced need for steroids.

13.10 Effect of Pharmacotherapy of Nasal Polyps on Bronchial Asthma

13.10.1 Corticosteroids

Oral corticosteroids are nowadays considered the most effective pharmacotherapy in NP (especially with concomitant asthma). Due to their potent, systemic anti-inflammatory effect, their use allows achieving concomitant asthma control. Short-term courses of oral corticosteroids (usually 3–4 times a year) effectively reduce size of NP ("medical polypectomy"). However, the effects of oral corticosteroids in NP are

short lasting, and regrowth of polyps occurs within weeks to months. Unfortunately, there are few controlled studies assessing the effect of those drugs in NP [46]. Prednisolone (50 mg) daily for 14 days significantly improved nasal symptoms and reduced polyp size, as noted with endoscopy [25].

Intranasal steroid sprays may slightly reduce the growth of minor NP and retard relapses following sinus surgery, but they do not improve sense of smell. Therapy of concomitant allergic rhinitis may improve control of asthma [10]. Resistance of NP to intranasal corticosteroids was linked to BHR or AIA appearance [8, 32, 34].

13.10.2 Leukotriene Inhibitors

As discussed above, cys-Lts are important mediators implicated in the pathogenesis of eosinophilic NP, especially in AIA [48, 63].

Leukotriene inhibitors are either leukotriene synthesis inhibitors, which act by blocking 5-lipoxygenase activity (zileuton) or leukotriene receptor antagonists (zafirlukast, montelukast, pranlukast). Antileukotrienes exert moderate systemic anti-inflammatory effect in lower respiratory tract, which was documented in many studies including patients with atopic, nonatopic, and exertional. Antileukotrienes might seem particularly beneficial in AIA, well known for overproduction of cys-LTs [14, 39, 60]. Allergic rhinitis with concomitant asthma is one of the recognized indications for antileukotrienes [10]. Unfortunately, although there are many studies evaluating the effect of antileukotrienes on asthma, only very few studies focused on NP. The current guidelines indicate that there is a need for larger, controlled trials assessing the role of antileukotrienes in NP [20].

13.10.3 Zileuton

In a double-blind placebo-controlled crossover study, the effects of 6-week treatment with zileuton (600 mg, four times daily) in 40 patients with AIA on nasal symptoms and PNIF were evaluated [14]. There was a statistically significant reduction in the VAS scores for loss of smell and rhinorrhea [14]. The subsequent open study has demonstrated beneficial effect of zileuton in 10 patients with CRS and NP [45].

13.10.4 Leukotriene Receptor Antagonists

Open studies have demonstrated beneficial effect of leukotriene receptor antagonists for subjective symptoms in NP [53, 65]. An open study investigated the response to montelukast in NP with or without aspirin hypersensitivity [53]. Montelukast treatment resulted in significant subjective improvement in 64% ATA and 50% AIA patients; however, objective changes in peak expiratory flows occurred only in ATA group [53]. Acoustic rhinometry, nasal inspiratory peak flows, and nitric oxide levels did not change significantly in any group [53]. More recently, a prospective double-blind study compared the efficacy of montelukast with beclomethasone nasal spray in 40 patients with NP after ESS [42]. Although montelukast attenuated itching, postnasal discharge, and headache more than did intranasal corticosteroid, there was no difference in the recurrence rate between both groups [42].

13.10.5 Aspirin Desensitization

A significant improvement of asthmatic symptoms, hospitalizations due to asthma exacerbations, and decrease in doses of corticosteroids following aspirin desensitization were demonstrated [38, 49, 60]. Number of sinus infections and the need of sinus surgery for NP decreased in those patients as well [38, 49, 60].

Intranasal L-ASA administration may bypass side effects of aspirin, but its effect seems to be limited to upper airways only [44].

13.10.6 Other Agents

There are only anecdotal reports concerning the use of anti-IgE treatment or macrolides in CRS with NP.

According to current guidelines, both NP and bronchial asthma are IL-5-driven disorders characterized by elevated local IgE levels and eosinophilic infiltration [3, 20, GINA 2007 revised]. Omalizumab, an anti-IgE agent, is indicated in severe asthma (GINA 2007 revised). A pilot study assessed the efficacy of omalizumab in atopic asthmatics with NP who underwent ESS [47]. Although there was no improvement in the sinus CT scores in either treatment group, the nasal

polyp scores significantly decreased in the anti-IgE group as compared to controls [47].

In addition to their well-recognized antimicrobial activity, macrolides exert a wide range of anti-inflammatory activities in CRS, NP, asthma, or CF [21]. Those agents regulate leukocyte function, increase mucociliary clearance, decrease nasal secretions and polyp size, attenuate BHR, and improve pulmonary function [21, 37, 54]. A beneficial effect of macrolides resulting in reduced NP size was linked with decreasing the levels of IL-8 [26, 66].

Given the common pattern of inflammation seen in eosinophilic NP and asthma, patients may best benefit from a therapeutic approach covering the entire airways rather than only a part. Oral corticosteroids, aspirin desensitization, and possibly anti-IL-5 therapy or macrolides may stand for a therapeutic alternative in NP.

Conflict of Interest

We declare that we have no conflict of interest.

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Take Home Pearls

- Nasal polyps afflict 2–4% of the general population, 5% of atopic asthmatics, and 13% of nonatopic asthmatics and over 50% of patients with aspirin induced asthma (AIA).
- Even in the absence of asthma, patients with NP are more likely to have bronchial hyperresponsiveness.
- In 70% of asthmatics, NP are diagnosed before asthma.
- Nasal polyps are generally more refractory to therapy in asthmatics than nonasthmatics, especially in patients with AIA.
- Most studies show some improvement in asthma with sinus surgery, but not all patients benefit and relapse is common.

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