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RESIDENT PHYSICIAN: Camysha Wright, MD, MPH
FACULTY PHYSICIAN: Jing Shen, MD
SERIES EDITORS: Francis B. Quinn, Jr., MD

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Introduction

Nasal polyposis is a chronic inflammatory disease of the upper airway characterized histologically by the infiltration of inflammatory cells like eosinophils or neutrophils. Nasal polyps represent edematous semitranslucent masses in the nasal and paranasal cavities, mostly originating from the mucosal linings of the sinuses and prolapsing into the nasal cavities. Etiology and pathophysiology are only partly understood, there is no valid classification of polyp subgroups to allow prediction of outcome after medical or surgical therapy, and recurrences are frequent regardless of treatment, making repeated surgical interventions necessary. Furthermore, surgical interventions may lead to unsatisfactory healing and may cause complications due to scar formation, because mucosal wound healing also may be impaired as a result of poorly defined factors in the inflamed mucosa. Several hypotheses have been put forward regarding the underlying mechanisms including chronic infection, aspirin intolerance, alteration in aerodynamics with trapping of pollutants, epithelial disruptions, epithelial cell defects/gene deletions (CFTR gene), and inhalant or food allergies.

The objectives of medical management of nasal polyposis are 1) to eliminate nasal polyps and rhinitis symptoms, 2) to reestablish nasal breathing and olfaction, and 3) to prevent recurrence of nasal polyps. Although antibiotics are used for infectious complications of nasal polyposis, only glucocorticosteroids (steroids) have a proven effect on the symptoms and signs of nasal polyps. Topically applied steroids are the therapeutic modality that has been best studied in controlled trials. It reduces rhinitis symptoms, improves nasal breathing, reduces the size of polyps and the recurrence rate, but it has a negligible effect on the sense of smell and on any sinus pathology. Topical steroids can, as long-term therapy, be used alone in mild cases, or combined with systemic steroids/surgery in severe cases. Systemic steroids, which are less well studied, have an effect on all types of symptoms and pathology, including the sense of smell. This type of treatment, which can serve a "medical polypectomy," is only used for short-term improvement due to the risk of adverse effects. Individualized management of nasal polyposis may use long-term topical steroids, short-term systemic steroids, as well as surgery, in various

combinations. Exactly how these therapies, which differ in their control of various symptoms, are optimally combined is not yet well established.

In the majority of nasal polyps, eosinophils comprise more than 60% of the cell population. Besides eosinophils, mast cells and activated T cells are also increased. An increased production of cytokines/chemokines like granulocyte/macrophage colony-stimulating factor, IL-5, RANTES and eotaxin contribute to eosinophil migration and survival. Increased levels of IL-8 can induce neutrophil infiltration. Increased expression of vascular endothelial growth factor and its upregulation by transforming growth factor-[beta] can contribute to the edema and increased angiogenesis in nasal polyps. Again, transforming growth factor-[beta] can modulate fibroblast function and thus contribute to eosinophil infiltration and stromal fibrosis. Other mediators like albumin, histamine and immunoglobulins IgE and IgG are also increased in nasal polyps. In addition, the local production of IgE in nasal polyps can contribute to the increased recurrence of nasal polyps via the IgE-mast cell-Fc [epsilon] RI cascade. Finally, mast cell/T cell-epithelial cell/fibroblast interactions can contribute to the persistent eosinophilic inflammation seen in polyps.

The diagnosis of nasal polyps is based on the finding of pale-gray, semitranslucent, round or bag-shaped mucosal protrusions from the sinuses into the nasal cavity, filled with gelatinous or watery masses. Most nasal polyps arise from the clefts of the middle nasal meatus and ethmoidal cells, prolapsing into the nose, with some polyps originating in the maxillary, sphenoid, or frontal sinuses. Polyps originating from the middle and superior turbinates may be seen in more severe disease, and those from the inferior turbinate are extremely rare.

Depending on the extent of polyp masses within the nasal cavities, patients develop various symptoms and complaints. The typical history is a “cold” that persisted over months or years, with nasal obstruction and discharge as the most prominent symptoms. With time, hyposmia or anosmia develop, and additional complaints such as the feeling of a “full head” are present. Anosmia is a typical symptom for nasal polyps, differentiating it from chronic sinusitis without polyposis, and may serve as a valid marker to estimate the duration and extent of disease. Interestingly, whereas chronic sinusitis is often associated with headache and facial pain, nasal polyposis itself rarely causes pain despite the fact that most of the sinuses, including the frontal sinuses, are opacified. Viral infections frequently cause prolonged episodes of severely obstructed nasal passages and colored secretions, probably because ventilation and drainage of the sinuses are decreased by the polyp masses, with subsequent bacterial infection. According to some investigations, infections may also cause a temporary growth of the polyps and, if persistent, may accelerate the disease course. Inhalant allergens do not seem to induce additional complaints. Patients also often report nasal congestion and discharge resulting from alcoholic beverages.

Because nasal polyps may represent a part of a systemic disease, adequate questions and further investigations may be necessary. Asthma and other lung diseases, aspirin sensitivity, Churg-Strauss syndrome, inhalant allergies, and CF must be considered.

With the introduction of rigid endoscopes into daily practice, nasal polyps are now discovered in earlier stages than they were 10 years ago. Although anterior rhinoscopy may detect large polyps, it is not considered sufficient to exclude polyps. Especially for the

differential diagnosis, an endoscopic investigation of the nose after topical decongestion is necessary. To investigate the extent of disease within the sinuses, a computer tomography (CT) scan with coronary sections is performed, with special reference to mucosal structures and the delicate anatomy of the sinuses. A CT scan is mandatory before sinus surgery may be considered, and CT must be available during surgery to inform the surgeon about anatomic variations. In addition, magnetic resonance imaging (MRI) may be helpful for the diagnosis of fungal disease and tumor or if intracranial extension of disease is suspected.

Classification

Nasal polyposis is not a consistent disease; on clinical grounds and based on etiology, histopathology, and recently mediator content as well, nasal polyps now may be subdivided into different groups. It is currently unclear, however, whether idiopathic polyps without involvement of the lower airways could develop into polyposis with concomitant asthma. Antrochoanal polyp, arising primarily from maxillary sinus and prolapsing into choana; a typically large, isolated, unilateral, cyst like noneosinophilic formation. Idiopathic unilateral or bilateral, mainly eosinophilic polyps without involvement of lower airways. Bilateral eosinophilic polyposis with concomitant asthma and/or aspirin sensitivity. Polyposis with underlying systemic disease (e.g., cystic fibrosis, primary ciliary dyskinesia, Churg-Strauss syndrome, Kartagener's syndrome).

To determine the extension of disease within the nose and the sinuses, endoscopic and CT-based staging systems have been proposed and partially validated. These systems may prove useful for medical communication and for the evaluation of therapeutic responses. The endoscopic staging system is mainly based on the assumption that polyp growth starts from the middle nasal meatus, then two-dimensionally extends toward the floor of the nose. However, the nasal cavity is a three-dimensional structure, which may have a negative impact on the reproducibility of this system by different investigators. The radiologic staging system includes all sinuses and the ostiomeatal complex bilaterally

Endoscopic Staging System for Nasal Polyposis

Score		Right	Left
0	No polyps present		
1	Polyps confined to middle meatus		
2	Polyps beyond middle meatus (reaching inferior turbinate or medial to middle turbinate)		
3	Polyps almost or completely obstructing nasal cavity		

Modified from Lund VJ, Kennedy DW: *Ann Otol Rhinol Laryngol* 140 (suppl 167):17, 1995.

About a century ago, an allergic etiology of nasal polyps was presumed but never firmly demonstrated.

Differential Diagnosis

Because the symptomatology of nasal polyps is rather nonspecific, nasal endoscopy needs to be performed to confirm the diagnosis and exclude other diseases. Nasal obstruction may also be caused by turbinate hypertrophy, chronic rhinosinusitis, or adenoid hypertrophy. Although nasal polyps have a characteristic appearance when investigated by nasal endoscopy, inverting papillomas and occasionally benign or malignant tumors or even meningoencephaloceles may be mistaken for nasal polyps. Any unilateral obstruction, nose bleeding, or crusting should be intensively investigated.

The management of nasal polyps may involve medical approaches, mainly based on the use of topical or systemic corticosteroids, and surgical procedures, from the extraction of polyps in the nasal lumen to radical ethmoidectomy in order to eradicate all polyp tissue. However, because nasal polyposis is a chronic disease with a high rate of recurrences in about one third of patients, surgical overtreatment and its sequelae should be avoided. Instead, a combined treatment strategy is recommended for long-term control of the disease.

The symptomatic efficacy of intranasal corticosteroids in patients with nasal polyps is well documented although modest. Symptoms such as nasal blockage, rhinorrhea, and occasionally hyposmia are reduced during treatment, but recurrence of symptoms occurs within weeks to months after treatment. The effects on nasal obstruction and polyp masses may also be documented by objective methods, such as peak nasal inspiratory flow, rhinomanometry, rhinometry, and smell tests. Topical corticosteroids may also reduce the incidence of polyp recurrences after surgery. However, topical corticosteroids may be insufficient in severe bilateral polyps, and polyp growth may be observed despite treatment.

Systemic corticosteroids, such as 32 mg of prednisolone initially with stepwise dose reduction during a 14-day to 20-day oral course, are extremely effective in reducing polyp size and symptoms. The suppression of gene transcription for many cytokines is a prominent action of glucocorticosteroids, including IL-5 and eotaxin. Because of these effects, recruitment and localization of inflammatory cells into polyp tissue are inhibited, as are their activation and protein synthesis. This has a prominent effect on numbers of nasal eosinophils, eosinophil products, and survival and may also affect plasma protein retention. However, polyps will recur rapidly in patients with severe disease, and little evidence thus far suggests that the natural course of the disease is influenced by long-term low-dose treatment regimes. Current studies focus on the effect of anti-IL-5 treatment in severe polyposis to circumvent the side effects induced by long-term steroid treatment.

Based on theoretic considerations, it has been proposed that antileukotriene therapy would be successful in patients with aspirin sensitivity or polyp recurrences after surgery. However, large-scale placebo-controlled studies have not yet been reported.

Antibiotics are indicated in the case of superimposed bacterial infection. Recently, macrolide antibiotics were suggested not only to decrease the virulence of colonizing bacteria but also to have antiinflammatory activities, leading to a significant reduction of polyp size paralleled by a decrease in local interleukin-8 (IL-8). Again, large-scale placebo-controlled studies have to be performed to test this hypothesis formally. However, the recent finding of a

possible role of SAEs as a pathogenic mechanism in nasal polyps may suggest the long-term use of antibiotics for primary treatment.

Sinus surgery, currently referred to as functional endoscopic sinus surgery (FESS), is a standard treatment with good functional results in patients resistant to medical treatment, avoiding radical surgical procedures. The aim is to remove polyp tissues in the nose and sinuses with preservation of anatomic structures and healthy mucosa. Extensive postoperative care and follow-up are required to preserve the postoperative results and to prevent regrowth of polyps. An individualized management regimen for nasal polyposis may combine long-term topical steroids, short-term systemic steroids, and surgery. In a 20-year follow-up study of 41 patients with nasal polyps, 85% of patients still suffered from the disease, with anosmia present in 61%. Eight subjects, including seven with aspirin sensitivity, had undergone 11 or more surgical procedures during the 20-year period. This study and others showing the high recurrence rate in nasal polyps clearly indicate the chronicity of the disease at least in this subgroup of patients and suggest a reserved surgical approach. Eradication of disease by surgery is an exception.

Surgical treatment of nasal polyps has declined in recent years as the benefits of medical treatment have become increasingly recognized. There is good evidence to support the use of corticosteroids both as a primary and post-operative treatment in the majority of patients. Other medical treatments require further evaluation before they could be considered a viable alternative to steroids. Assessment of the literature regarding surgical intervention is difficult and there is little evidence on which to base a surgical treatment philosophy.

Blomqvist et al (2001) compared the effect of medical treatment versus combined surgical and medical treatment on olfaction, polyp score, and symptoms in nasal polyposis. They evaluated thirty-two patients with nasal polyposis and symmetrical nasal airways were randomized to unilateral endoscopic sinus surgery after pretreatment with oral prednisolone for 10 days and local nasal budesonide bilaterally for 1 month. Postoperatively, patients were given local nasal steroids (budesonide). Patients were evaluated with nasal endoscopy, symptom scores, and olfactory thresholds. They were followed for 12 months. They found that the sense of smell was improved by the combination of local and oral steroids. Surgery had no additional effect. Symptom scores improved significantly with medical treatment alone, but surgery had additional beneficial effects on nasal obstruction and secretion. After surgery, the polyp score decreased significantly on the operated side but remained the same on the unoperated side. Twenty-five percent of the patients were willing to undergo an operation also on the unoperated side at the end of the study. They concluded that medical treatment seems to be sufficient to treat most symptoms of nasal polyposis. When hyposmia is the primary symptom, no additional benefit seems to be gained from surgical treatment. If nasal obstruction is the main problem after steroid treatment, surgical treatment is indicated.

Fungus has also been considered to be involved in the development of AFS, though there is no consensus on its involvement or in the use of amphotericin B rinses to aid with nasal polyposis. Richetti et al (2002) looked into amphotericin B nasal rinses as a possible adjuvant for the treatment of nasal polyposis and stated that a direct effect on the integrity of the cell membrane could not be excluded. However, Weschta et al (2004) compared the effects of amphotericin B versus control nasal spray on chronic rhinosinusitis in a double-blind, randomized clinical trial. Patients with chronic rhinosinusitis were administered 200 µL per

nostril amphotericin B (3 mg/mL) or saline nasal spray 4 times daily over a period of 8 weeks. The response rate, defined as a 50% reduction of pretreatment computed tomography score, was the primary outcome variable. Additional outcome variables included a symptom score, a quality of life score, and an endoscopy score. Before and after treatment, nasal lavages were pretreated with dithiothreitol and examined for fungal elements by PCR and standard culture techniques. They found that nasal amphotericin B spray in the described dosing and time schedule was ineffective and deteriorated patient symptoms.

Hissaria et al studied the efficacy of a short course of oral prednisolone in ameliorating the symptoms of sinonasal polyposis, as well as reducing mucosal inflammation assessed by means of nasendoscopy and magnetic resonance imaging (MRI). Subjects with symptomatic endoscopically diagnosed sinonasal polyposis received 50 mg of prednisolone daily for 14 days or placebo. Outcome was quantified by using the modified 31-item Rhinosinusitis Outcome Measure questionnaire, physician's assessment, nasendoscopy with photography, and MRI. There were 20 subjects in each treatment group. Only the prednisolone-treated group showed significant improvement in nasal symptoms ($P < .001$). The Rhinosinusitis Outcome Measure score improved in both groups, but the prednisolone-treated group had significantly greater improvement than the placebo group ($P < .001$). Objectively, there was significant reduction in polyp size, as noted with nasendoscopy ($P < .001$) and MRI ($P < .001$), only in the prednisolone-treated group. The outcome measures correlated with each other; the highest level of correlation was between the objective measures of nasendoscopy and MRI ($R^2 = 0.76$, $P < .001$). There were no significant adverse events. This trial clearly establishes clinically significant improvement in the symptoms and pathology of sinonasal polyposis with a short course of systemic corticosteroids. MRI scanning and quantitative nasendoscopic photography are objective and valid tools for assessing the outcome of treatment in this condition. A 14-day course of 50 mg of prednisolone is safe and effective therapy for symptomatic nasal polyposis.

Macrolides have been used for decades as an important chemotherapeutic agent in the treatment of infectious diseases. In the last 10 years there has also been increasing interest in the interaction between macrolide antibiotics and the immune system. However there have been, especially from Japan, a number of clinical reports stating that long-term, low-dose macrolide antibiotics are effective in treating chronic sinusitis incurable by surgery or glucocorticosteroid treatment, with an improvement in symptoms varying between 60% and 80% in different studies. In animal studies macrolides have increased mucociliary transport, reduced goblet cell secretion and accelerated apoptosis of neutrophils, all factors that may reduce the symptoms of chronic inflammation. There is also increasing evidence in vitro of the anti-inflammatory effects of macrolides. Several studies have shown macrolides to inhibit interleukin gene expression for IL-6 and IL-8 and also to inhibit the expression of intercellular adhesion molecule essential for the recruitment of inflammatory cells. There is also evidence in vitro, as well as clinical experience, showing that macrolides reduce the virulence and tissue damage caused by chronic bacterial colonization without eradicating the bacteria. The benefit of long-term, low-dose macrolide treatment seems to be that it is, in selected cases, effective when steroids fail. The exact mechanism of action is not known, but it probably involves downregulation of the local host immune response as well as a downgrading of the virulence of the colonizing bacteria.

Erythromycin (EM) was originally recovered from a soil sample from the Philippine archipelago. It is the metabolic product of a strain of *Streptomyces erythreus*. Clarithromycin

(CAM), roxithromycin (RXM), and azithromycin (AZM) are new semi-synthetic derivatives of EM. There have been many Japanese studies reporting the use of macrolides for sinusitis and nasal polyposis. Hashiba and Baba (1996) studied 45 adult patients with chronic sinusitis, 44% of whom had had previous sinus surgery. They were treated with 400 mg/day CAM for 8 or 12 weeks. Improvement in symptoms and rhinoscopic findings were noted in 71.1% of the patients at the end of the treatment period. The study demonstrated the slow onset of macrolide therapy. After 2 weeks of treatment only 5 % of patients indicated improvement, after 4 weeks 48% were improved, after 8 weeks 63% were improved and after 12 weeks 71% were improved. It concluded that CAM was as effective as EM. A study of nasal polyps with chronic sinusitis was presented by Ichimura et al in 1996. Treatment with 150 mg RXM per day for at least 8 weeks showed reduction in nasal polyps by 52%. With the addition of astelin (azelastine) 1 mg twice daily, an inhibitor of mediator release, another 20 patients were evaluated. Azelastine augmented the rate of improvement to 68% compared to RXM alone but the result wasn't significant. Smaller polyps were more likely to decrease in size, but some larger polyps also markedly decreased in size.

Although nasal polyposis is a multifactorial disease with several different etiological factors, chronic persistent inflammation is undoubtedly a major factor irrespective of the etiology. Although antibiotics are used for infectious complications of nasal polyposis, only glucocorticosteroids (steroids) have a proven effect on the symptoms and signs of nasal polyps. Macrolides may play a role in the future in management of nasal polyps but further studies must be conducted in this area.

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