Medical Management of Nasal Polyposis

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Grand Rounds Presentation
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Background

The term nasal polyposis comprises all types of nasal polyps which emerge as blue-gray protuberances in the area of:

- the ethmoid bone,
- middle meatus,
- nose and
- middle turbinate
Background

- Nasal polyposis
  - characterized by eosinophil inflammation,
  - accompanied by acetylsalicylic intolerance in up to 25% of cases
- 40% of cases of nasal polyposis are associated with intrinsic asthma
- Samter’s triad (nasal polyps, aspirin allergy, and asthma)
- Associations have also been described between Churg-Strauss syndrome (a form of eosinophilic immunovasculitis) and eosinophilic nasal polyposis
Background

- 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.
Background

Several hypotheses 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.
Anatomy

- Histologically polyps are characterized by
  - edema or fibrosis,
  - reduced vascularization,
  - reduced number of glands and
  - nerve endings in the presence of often damaged epithelium
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.
Pathophysiology

- 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.
Pathophysiology

- Increased expression of VEGF and its upregulation by transforming growth factor-[beta] contribute to edema and increased angiogenesis in nasal polyps.
- Transforming growth factor-[beta] modulate fibroblast function
  - eosinophil infiltration and stromal fibrosis.
- Other mediators like albumin, histamine and immunoglobulins IgE and IgG are also increased in nasal polyps.
History and Physical Exam

- Diagnosis is based on finding of pale-gray, semitranslucent, round or bag-shaped mucosal protrusions from the sinuses into the nasal cavity, filled with gelatinous or watery masses.

- Polyps originating from the middle and superior turbinates may be seen in more severe disease, and those from the inferior turbinate are extremely rare.
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.
History and Physical Exam

The typical history is
- a “cold” that persisted over months or years,
- nasal obstruction and discharge 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,
- may serve as a valid marker to estimate the duration and extent of disease.

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.
History and Physical Exam

- 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.
Endoscopic Staging System for Nasal Polyposis

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No polyps present</td>
</tr>
<tr>
<td>1</td>
<td>Polyps confined to middle meatus</td>
</tr>
<tr>
<td>2</td>
<td>Polyps beyond middle meatus (reaching inferior turbinate or medial to middle turbinate)</td>
</tr>
<tr>
<td>3</td>
<td>Polyps almost or completely obstructing nasal cavity</td>
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Radiological Evaluation

- 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.
Differential Diagnosis

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 objectives of medical management of nasal polyposis

1) to eliminate nasal polyps and rhinitis symptoms,
2) to reestablish nasal breathing and olfaction, and
3) to prevent recurrence of nasal polyps.
Available Treatments for sinusitis, chronic obstruction

- Sinus ventilation and drainage
- Management of allergies
- Saline irrigation
- Mucolytics
- Antihistamines
- Leukotrienes
- Corticosteroids
- Topical corticosteroids
- Decongestants
- Topical decongestants
Sinus ventilation and drainage

- Oral hydration
- Saline sprays
- Humidification
- Decongestants
- Mucolytics
Management of allergies

- Allergen avoidance
  - history or positive skin prick tests
- Saline irrigation
- Antiinflammatory therapy
- Antihistamine
- Leukotriene Receptor Antagonists
- Decongestant
Saline irrigation

- Increase mucociliary flow rates
- Brief vasoconstrictive effect
- Mechanically rinse
- Adding baking soda
  - Alkaline medium leads to thinning of mucus
  - An acidic medium creates a more viscous (gel) mucus
Mucolytics

- Guaifenesin
- High doses are required for obtaining an effect on mucous
  - Emesis and abdominal pain
Antihistamine

- Inhibition of histamine receptor
- Ineffective in relieving chronic nasal congestion
- First-generation antihistamines
  - Anticholinergic
    - adverse effects such as drowsiness
    - Leads to drying of secretions
Second-generation antihistamines

- Higher affinity to histamine receptors and increased potency
- No anticholinergic effect
- Cetirizine
  - Block other mediator release such as that of leukotrienes and kinins
  - Inhibit monocyte and lymphocyte chemotaxis
  - Beneficial in the treatment of chronic congestion
Leukotriene

- More potent than histamine in triggering nasal allergic inflammation
- Leukotriene Receptor Antagonists
  - Effective in allergic rhinitis
  - Beneficial effects for the indication of chronic rhinosinusitis
Corticosteroid

- Immunomodulator
  - Stabilize mast cells
  - Block formation of inflammatory mediators
  - Inhibit chemotaxis of inflammatory cells
- Short courses of systemic corticosteroids
  - Tx severe nasal mucosal congestion in allergic patients
Corticosteroid

- 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.
  - 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.
Corticosteroid

- 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.
Corticosteroid

- Contraindications
  - Diabetes
  - Peptic ulcer disease
  - Glaucoma
  - Severe hypertension
  - Advanced osteoporosis
Topical corticosteroids

- Improve patency of the ostiomeatal complex
  - reduction in mucosal swelling
- Inhibit both immediate and late-phase reactions to antigenic stimulation (After 7 days of treatment)
- 90% of patients with allergic rhinitis will experience improvement
Topical corticosteroids

- Common adverse effects
  - nasal irritation, mucosal bleeding, and crusting
  - propylene glycol contained in the preparations
- Alleviated by switching to a aqueous delivery system
- Concomitant nasal saline used lessen or eliminate the adverse effects
Decongestants

- vasoconstriction of dilated mucosal blood vessels (α-adrenergic agonists)
- symptomatic relief of nasal congestion
- No therapeutic efficacy for the treatment of sinusitis
Topical Decongestants

- Phenylephrine & oxymetazoline
- Rhinometric analysis
  - Rebound vasodilation as early as 3 days
- Rhinitis medicamentosa
  - after 10 days to 2 weeks
Macrolide

- Antiinflammatory effect
- Accumulate in inflammatory cells >100X higher than concentrations in extracellular fluid
Macrolide Inmunomodulator effect

- Macrolide antibiotics targets cytokine production
  - Decreased IL-5, IL-8, GM-CSF, TGF-β, IL-6, IL-8, TNF-α
- Reduced expression leukocyte adhesion molecules
- Accelerate neutrophil apoptosis
- Impaired neutrophil oxidative burst
- Decrease secretion and improve mucociliary clearance
- Inhibited release of elastase, protease, phospholipase C, and eotaxin A by *P aeruginosa*
Macrolide

- Long-term, low-dose macrolides for treatment of CRS (primarily in Japan)
- Clarithromycin is the macrolide most studied in CRS
- Azithromycin lack studies in CRS
- Long term use is 3-12 month
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 clarithromycin (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 result wasn’t significant.

Smaller polyps were more likely to decrease in size, but some larger polyps also markedly decreased in size.
Short course of systemic corticosteroids in sinonasal polyposis: A double-blind, randomized, placebo-controlled trial with evaluation of outcome measures

- Hissaria et al (EBM A)
  - the efficacy of a short course of oral prednisolone in ameliorating the symptoms of sinonasal polyposis,
  - 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 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.
Short course of systemic corticosteroids in sinonasal polyposis A double-blind, randomized, placebo-controlled trial with evaluation of outcome measures

- 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 ($R^2 = 0.76$, $P < .001$).
Short course of systemic corticosteroids in sinonasal polyposis A double-blind, randomized, placebo-controlled trial with evaluation of outcome measures

- 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.
Randomised controlled study evaluating medical treatment vs surgical treatment in addition to medical treatment of nasal polyposis

- Blomqvist et al (2001) (EBM B) 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.
Randomised controlled study evaluating medical treatment vs surgical treatment in addition to medical treatment of nasal polyposis

- 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.
Effect of anti-fungal nasal lavage with amphotericin B on nasal polyposis

- 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.

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.

They found that nasal amphotericin B spray in the described dosing and time schedule was ineffective and deteriorated patient symptoms.
Conclusions

- Nasal polyposis is a multifactorial disease with several different etiological factors.
- 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.


