

Nasal Polyposis: Current Trends

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Abstract Nasal polyps (NP) are one of the most common inflammatory mass lesions of the nose, affecting up to 4% of the population. They present with nasal obstruction, anosmia, rhinorrhoea, post nasal drip, and less commonly facial pain. Their etiology remains unclear, but they are known to have associations with allergy, asthma, infection, fungus, cystic fibrosis, and aspirin sensitivity. However, the underlying mechanisms interlinking these pathologic conditions to NP formation remain unclear. Also strong genetic factors are implicated in the pathogenesis of NP, but genetic and molecular alterations required for its development and progression are still unclear. Management of NP involves a combination of medical therapy and surgery. There is good evidence for the use of corticosteroids (systemic and topical) both as primary treatment and as postoperative prophylaxis against recurrence, but the prolonged course of the disease and adverse effects of systemic steroids limits their use. Hence several new drugs are under trial. Surgical treatment has been refined significantly over the past 20 years with the advent of endoscopic sinus surgery and, in general, is reserved for cases refractory to medical treatment. Recurrence of the polypoid is common with severe disease recurring in up to 10% of patients. Over the last two decades, increasing insights in the pathophysiology of nasal polyposis opens perspective for new pharmacological treatment options, with eosinophilic inflammation, IgE, fungi and *Staphylococcus aureus* as potential targets. A better understanding of the pathophysiology underlying the persistent inflammatory state in NP is necessary to ultimately develop novel

pharmacotherapeutic approaches. In this paper we present the newer treatment options available for better control and possibly cure of the disease.

Keywords Nasal polyps · Pathophysiology · New pharmacological options · Surgery

Introduction

Nasal polyposis is an unpleasant disease for a patient, which severely effects his quality of life. Despite its easy diagnosis, it is a challenge for otorhinologists, because of its poorly understood etiopathogenesis, poor impact of therapeutic intervention and frequent recurrences. It is a multifactorial condition which is often associated with many diseases and pathogenic disorders, such as allergy, infection, allergic fungal sinusitis, cystic fibrosis, asthma, and aspirin intolerance. However, the underlying mechanisms interlinking these pathologic conditions to NP formation remain unclear. Although the exact etiology of nasal polyposis is still not revealed, insights in the pathogenesis have largely expanded over the last years. Increasing insights in the pathophysiology of nasal polyposis opens perspective for new pharmacological treatment options, with eosinophilic inflammation, IgE, fungi and *Staphylococcus aureus* as potential targets. This paper aims to summarize current trends in all aspects of management of NP.

Pathogenesis

NPs are outgrowths of nasal mucosa which are smooth, semi translucent, gelatinous and pale, mainly situated in the

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middle meatus, originating from mucous membrane of the ostiomeatal complex, probably because of release of pro-inflammatory cytokines from epithelial cells as a result of contact between two surfaces of mucosa at this narrow region. Air turbulence and pressure differential may also have an influence. Various other important factors like genetic factors, bacteria, fungi, biofilm formation, etc. have been implicated, and have been discussed in subsequent paragraphs. Histo-morphological characterization of polyp tissue reveals frequent epithelial damage, a thickened basement membrane, and oedematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands, but virtually no neural structure. Polyps show an increased number of mast cells, eosinophils, T lymphocytes, cytokines, chemokines, interleukins, TNF- α and adhesion molecules.

Role of Genetic Factors in Pathogenesis

During the past two decades, many studies have been performed to determine differential gene expression profiles between NP and normal nasal tissues, in order to identify susceptible genes that are associated with NP-related traits. A number of genetic association studies found a significant correlation between certain human leukocyte antigen (HLA) alleles and NP. The risk of developing NP can be as high as 5.53 times in subjects with HLA-DQA1*0201-DQB1*0201 haplotype [1]. The development and persistence of mucosal inflammation in NPs have been reported to be associated with numerous genes and potential single nucleotide polymorphisms. A recent study showed that in NP tissues, 192 genes were upregulated by at least twofold, and 156 genes were downregulated by at least 50% in NP tissues as compared to sphenoid sinuses mucosa [2]. It has also been postulated that an abnormal mucosal immune response underlies disease pathogenesis [3]. There are a number of genes which are involved in epithelial barrier maintenance and repair in the inflammatory state of NP. For example, carbonic anhydrase (CA) is a zinc metalloenzyme that participate in the biological processes of various fluid transporting epithelia, including ion and water transport. A decreased expression level of CA was found to be associated with impaired electrolyte and water transport across the epithelial cell, which will result in oedema of NP tissue [4]. Identifying the causal genes and variants in NP is important to the path towards improved prevention, diagnosis and treatment of NPs.

Role of Fungus

Among the possible etiologies, fungi have gained wide attention in recent years. Though fungal particles are

present in sinonasal mucosa of healthy subjects too, but they act as antigens in mucosa of sensitized individuals, resulting in recruitment of inflammatory cells—namely eosinophils—and release of major basic protein (MBP), which finally causes mucosal damage and superinfection by migration of other inflammatory cells into that location [5]. This fungal antigen is derived from the germinating fungal spores and hyphae. This inflammatory reaction is different from the one seen in response to a fungus ball which is more of an irritative inflammation, like a foreign body reaction, i.e., giant cells, and not an eosinophilic inflammation, which is present in nasal polyposis [6]. *Aspergillus* and *Alternaria* are commonest fungi species implicated in the pathogenesis of nasal polyposis [7].

Role of Biofilms

Microorganisms like bacteria and fungi exist in two main forms in the sinonasal cavities: as free-floating planktonic replicating cells and in biofilms. Biofilms are defined as organized communities of collaborating microorganisms that are attached to an inert or living surface contained in a self-produced polymeric matrix primarily composed of exopolysaccharides, nucleic acids, and proteins [8]. The structural nature of biofilms and the characteristics of sessile cells produce resistance against antimicrobial agents, resulting in an environment that affords protection against adverse conditions and the host's defenses [9]. The bacteria in these biofilms, while protected from host defenses and antibiotics, actively metabolize and produce endotoxins and other virulence factors. This may perpetuate an inflammatory host response, even in the absence of culturable planktonic bacteria and lead to chronic inflammation [10]. Traditional antimicrobial treatments that target single microbial cells within biofilms will never be able to eliminate them. Therefore, antibiofilm therapies that target the entire biofilm as a complex multicellular organism or prevent unique, biofilm-specific processes are needed to fight biofilm infections.

Management of Sinonasal Polyposis

Therapy for NP involves a combination of observation, medical, and surgical treatments depending on individual case assessment. The aims of treatment are to eliminate or significantly reduce the size of the NP resulting in relief of nasal obstruction, improvement in sinus drainage, restoration of olfaction and taste. Treatment of Surgical procedures alone is insufficient to treat the underlying inflammation of the nasal mucosa. Supplementary medical treatment is always necessary to prevent recurrence.

Medical Management

Intranasal glucocorticoids constitute presently the best treatment of NP. They decrease polyp size, improve nasal airway patency, improve symptoms of rhinitis like rhinorrhoea, sneezing and nasal blockage, delay the recurrence of polyps after surgery and postpone the need for a new surgery [11]. The unusually wide range of GC actions can be explained by GC receptors present in three cell compartments: nucleus, cytoplasm, and plasma membrane. Both topical and systemic glucocorticoids may affect the eosinophil function by both directly reducing eosinophil viability and function or indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells [12]. Systemic steroids are reserved for advanced or refractory cases particularly when allergy is present and it results in relatively rapid short-term dramatic improvement, nasal symptoms and endoscopic findings (medical polypectomy). Simple saline nasal douching to help cleanse the nose prior to topical medications is beneficial as it improves nasal mucociliary clearance. Corticosteroids should be used with caution in ‘at-risk groups’ particularly patients with diabetes, uncontrolled hypertension, and peptic ulcer disease.

Role of Leukotrienes Antagonists

Leukotrienes (LTs) and prostaglandins are products of arachidonic acid metabolism, and are key mediators in acute and chronic inflammatory diseases of the airways. Leukotriene levels have been shown to be elevated in patients with sinonasal polyposis and sinusitis. Recent studies have shown, an objective alleviation, or at least stabilization, of sinonasal polyposis after use of short-term oral corticosteroid therapy combined with the LT synthesis inhibitor zileuton or the LT receptor antagonist zafirlukast and montelukast as maintenance therapy [13]. These improvements are probably based on the control of NP inflammation and possibly of polyp growth. So short-term oral corticosteroid therapy combined with montelukast in a daily dosage of 10 mg as maintenance therapy in controlling symptoms of severe sinonasal polyposis has been proven very effective. Also, an additional 3 months of montelukast therapy combined with intranasal and inhaled corticosteroids produces subjective and objective improvements in nasal symptoms and function as well as significant improvements in lung function in patients with nasal polyposis [14].

Role of *S. aureus* and Concept of Superantigens

Evidence accumulates that *S. aureus* colonizes chronic rhinosinusitis with, but not without polyps, with significantly

increased prevalence. The germs release enterotoxins, which act as superantigens and induce a topical multiclonal IgE formation as well as a severe, possibly steroidinsensitive eosinophilic inflammation [15]. Recently, *S. aureus* could be demonstrated to reside intraepithelially, and potentially to release superantigens into the tissue from within the epithelial cells. An immune defect, either in the innate or adaptive immunity, might be responsible for this phenomenon. Follicle-like structures and lymphocyte accumulations, specifically binding enterotoxins, can be found within the polyp tissues, giving rise to local IgE formation. The superantigen-induced immune response also leads to a modulation of the severity of the eosinophilic inflammation, and may be linked to lower airway co-morbidity in polyp patients. IgE antibodies to enterotoxins can be found in the majority of aspirin-sensitive polyp tissues, associated with a substantial increase in eosinophilic cationic protein (ECP) and IL-5 [16].

Role of Antibiotics

Based on the concept of *S. aureus* intraepithelial colonization, studies have been done to support the use of antibiotics along with corticosteroids to treat patients with NP. Recent studies have shown that oral doxycycline (200 mg on the first day, followed by 100 mg once daily) for 20 days has shown a significantly decreased NP size, reduced levels of myeloperoxidase, ECP, and matrix metalloproteinase 9 in nasal secretions [17].

Role of Anti IgE Therapy

Based on the concept of *S. aureus* derived enterotoxins acting as superantigens, massive IgE formation takes place within the airways. Because of the multiclonality, a range of allergens could possibly maintain a constant degranulation of mast cells present in the polyp tissue, which may contribute to disease severity. Omalizumab counteracts these interactions by reducing serum levels of free IgE. Therapy targeted at IgE also interferes with its binding to the low-affinity receptors inhibiting the amplification of the Th2-type response [18]. The high costs of treatment with omalizumab, the high frequency of NP, as well as the current lack of data concerning safety in long-term application of omalizumab has to be borne in mind and further studies have to be conducted [19].

Role of CMC Foam

Recurrence of nasal polyposis after endoscopic sinus surgery can be difficult to manage. Topical steroid sprays and

irrigations may not provide adequate treatment and systemic steroid therapy is limited by side effects. Steroid-infused carboxymethylcellulose (CMC) foam as a treatment for recurrence of chronic rhinosinusitis with nasal polyposis after endoscopic sinus surgery has been tried. Four milliliter of CMC foam hydrated with triamcinolone, 40 mg/ml is placed endoscopically into the ethmoid cavities bilaterally. Statistically significant endoscopic results were obtained regarding improvement in symptoms and endoscopic findings in patients with recurrent sinonasal polyposis after endoscopic sinus surgery [20].

Tamoxifen

Possible future perspectives in sinonasal polyposis include inhibition of human mast cell proliferation by tamoxifen. A study by Duffy et al. [21] suggests that tamoxifen might be useful in the treatment of mast cell-mediated diseases. Further studies are needed to prove its efficacy.

Role of Intranasal Furosemide

The best therapeutic approach to relapse of nasal polyposis is to interfere with the early phase of NP development. A key element in this context is the edematous infiltrate. Manipulation of this target may be effective in preventing relapses after surgery. According to this hypothesis, the genesis of nasal polyposis and their relapse is the development of edema secondary to increased plasma and water absorption into the lamina propria of the NP tissue [22]. The topical use of furosemide, a loop diuretic and inhibitor of the potassium and sodium chloride cotransporter channels, at the basolateral surface of the respiratory epithelial cell may result in a decrease in sodium absorption and an ultimate decrease in water absorption. Therefore, furosemide can cause a chemical gradient between the submucosa and the luminal surface of the respiratory epithelium and lead to an increased absorption of sodium and water. This would effectively dehydrate the surface of the respiratory epithelial cell [23]. Furosemide also has a protective effect with its ability to alter prostaglandin (PG) synthesis by the airway epithelium. It has shown to cause a marked reduction in both basal and arachidonic acid stimulated production of PGE2 and PGF2 alpha [24]. In the recent studies, furosemide is diluted in physiological solution (2 ml furosemide and 2 ml isotonic sodium chloride solution) administered as nasal puffs (2 puffs per day per nostril, each puff corresponding to 50 µg) for every alternate month for the first 2 years (total treatment, 6 months/year). During the next 3 years, treatment is given for 1 month and then interrupted for 2 months (total treatment, 4 months/year). After 5 years of treatment, furosemide

was administered for 1 month twice a year. Examination of patients every 6 months (complete ear, nose, and throat examination, active anterior rhinomanometry, AR, and nasal endoscopy) revealed that 17.5% of patients treated with furosemide had relapses, compared with 24.2% in the mometasone group and 30.0% in the untreated group [25]. Also the severity of recurrence is much less. As there are no long-term side effects, furosemide can be used as a valid therapeutic tool for the prevention of CHS–NP as an alternative to the use of topical corticosteroids, which have some clinical adverse effects on the nasal mucosa like epistaxis and septal perforation.

Role of Amphotericin-B NASAL Wash

With the discovery of the possible role of fungi in nasal polyposis, antifungal medical therapy has been an appealing and promising alternative in maintaining treatment following FESS to reduce recurrence and its severity in polyposis patients [26, 27]. Amphotericin B is a natural polyene antifungal agent which binds to ergosterol, a component of cell walls of most fungi, leading to formation of ion channels and cell death; it may also act secondarily through oxidative damage to fungal cell membranes through creation of free radicals from its own oxidation [28]. It is hypothesized that topical intranasal application of Amphotericin B can decrease the fungal load in the sinonasal region, thereby decreasing the local eosinophilic inflammatory reaction to fungal antigens seen in many chronic rhino-sinusitis with or without nasal polyposis patients [29, 30]. Amphotericin B is poorly absorbed through the gut when ingested orally, therefore there is little or no potential for systemic exposure to the drug when administered by the topical intranasal route [31]. Direct mucosal administration of intranasal amphotericin B is found to reduce the inflammatory mucosal thickening by CT scan, the disease stage by endoscopy, and an intranasal marker of eosinophilic inflammation, EDN [32]. Patients are instructed to apply 20 ml amphotericin B solution (250 mg/ml dissolved in sterile water) to each nostril twice a day by using a bulb syringe and pointing the tip toward the middle meatus region after bending their heads laterally to the side being irrigated. As exposure to light and room temperature reduces the antifungal potency in reconstituted amphotericin B in a time-dependent manner, so a higher concentration of amphotericin B (250 mg/ml) is used, but if it is possible for patients to refrigerate the solution, a dose of 100 mg/ml can be used [29].

Surgical Management

Surgical therapy is reserved for cases refractory to medical treatment. In general, patients are treated medically in the

primary care setting before consideration of surgical procedures by an otolaryngologist. Endoscopic sinus surgery is now the mainstay of treatment for NP [33, 34], though no single surgical technique has proved to be entirely curative and the recurrence rate is around 5–10% [35, 36]. Concurrent use of micro debrider enables accurate removal of NP whilst preserving normal anatomical structures such as the turbinates. Thorough knowledge of sinus anatomy, combined with preoperative imaging helps to avoid major complications such as blindness and CSF rhinorrhoea. Also the use of computer-aided surgery (CAS) technology, which allows a direct comparison of the intraoperative anatomy with preoperative imaging information furthers the operative accuracy. After a registration and calibration process, the surgeon may point to a specific structure with the CAS instrument and then view the location of the instrument tip on the CT image [37, 38]. The use of CAS systems may allow for more precise dissections and greater rates of sinus patency outcomes and fewer complications [39]. It is important postoperatively to regularly douche the nasal cavity with saline to prevent crusting and adhesions [40]. Topical intranasal steroids are also a routine part of after surgery care to prevent recurrence [41].

Conclusion

With improvement in the management protocols and further research, nasal polyposis would no longer remain a challenge for otorhinolaryngologists. Future studies are needed to identify the key factors underlying the development or formation of NP and to investigate the interactions between genetic, local and environmental factors that influence the complex traits of this disease. Identifying the causal factors and variants in NP is important to the path towards improved prevention, diagnosis and treatment of NPs.

Conflict of interest None.

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