

AN OVERVIEW OF SINONASAL POLYPOSIS: A PROSPECTIVE STUDY*Kabikanta Samantaray¹, Nishikanta Pradhan², Rudranarayan Biswa³*¹Associate Professor, Department of ENT, Kalinga Institute of Medical Sciences, Bhubaneswar.²Senior Resident, Department of ENT, Kalinga Institute of Medical Sciences, Bhubaneswar.³Professor, Department of ENT, Kalinga Institute of Medical Sciences, Bhubaneswar.**ABSTRACT****INTRODUCTION**

Sinonasal polyposis, one of the most common inflammatory mass lesions of the nose affecting up to 40% of the population. They present with nasal obstruction, anosmia, rhinorrhoea, post-nasal drip, and less commonly headache. Their aetiology remains unclear, but they are known to have associations with allergy, asthma, infection, fungus, cystic fibrosis, and aspirin sensitivity. Strong genetic factors are implicated in the pathogenesis of SNP, but genetic and molecular alterations required for its development and progression are still unclear. Management of SNP involves a combination of conservative treatment and surgical treatment. There is good evidence for the use of corticosteroids (systematic and topical), both as primary treatment and as postoperative prophylaxis against recurrence, but the prolonged course of the disease and adverse effect of systematic steroid limits their use. 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 polyposis 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 prospective 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 SNP is necessary to ultimately develop novel pharmacotherapeutic approaches. Here, we present the newer treatment options available for better control and possibly cure of the disease.

KEYWORDS

Sinonasal polyps, Pathophysiology, New pharmacological options, Surgery.

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INTRODUCTION: Sinonasal Polyposis 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 mechanism interlinking these pathologic conditions to SNP formation remain unclear. Although, the exact aetiology of sinonasal polyposis is still not revealed, insights in the pathogenesis have largely expanded over the last years. Increasing insights in the pathophysiology of sinonasal polyposis opens prospective for new pharmacological treatment options, with eosinophilic inflammation, IgE, fungi and staphylococcus aureus as potential targets. This study aims to summarise current trends in all aspects of management of SNP.

PATHOGENESIS: SNPs are outgrowths of nasal mucosa which are smooth, semitranslucent, gelatinous pale, mainly situated in the middle meatus, originating from mucous membrane of the ostiomeatal complex, probably because of release of proinflammatory 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. Other important factors like genetic factors, bacteria, fungi, biofilm formation, etc. have been implicated, and have been discussed in subsequent paragraphs. Histomorphological characterisation 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 cell, eosinophils, T lymphocytes, cytokines, chemokines, interleukins, TNF- and adhesion molecules.

Role of Genetic Factors in Pathogenesis: A number of genetic association studies found a significant correlation between certain human leukocyte antigen (HLA) alleles and SNP. The risk of developing SNP 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 SNPs have been reported to be associated with numerous genes and potential single nucleotide polymorphisms. A recent study showed that in SNP tissues, 192 genes were up regulated by at least two folds, and 156 genes were down regulated by at least 50% in SNP tissues as compared to sphenoid sinus 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 SNP. As an example, carbonic

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anhydrase (CA) is a zinc metalloenzyme that participates 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 SNP tissue.^[4] Identifying the causal genes and variants in SNP is important to the path towards improved prevention, diagnosis and treatment of SNPs.

Role of Fungus: Amongst the possible aetiologies, 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 sensitised individuals, resulting in recruitment of inflammatory cells—namely eosinophils and release of major basic protein (MBP), which finally causes mucosal damage and super infection 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 sinonasal polyposis.^[6] *Aspergillus* is the commonest fungi species implicated in the pathogenesis of sinonasal polyposis.^[7]

Role of Biofilms: Microorganisms like bacteria and fungi exist in two main forms in the sinonasal cavities: As free-floating planktonic replicating cell and in biofilms. Biofilms are defined as organised 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 defences.^[9] The bacteria in these biofilms, while protected from host defences and antibiotics, actively metabolise 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: Treatment for SNP involves a combination of observation, medical and surgical treatments according to individual case assessment. The aims of treatment are to eliminate or significantly reduce the size of the SNP 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 SNP. 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 usually 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 Leukotriene Antagonist: 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 stabilisation 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 improvements in nasal symptoms and function as well as significant improvements in lung function in patients with sinonasal polyposis.^[14]

Role of *S. aureus* and Concept of Superantigens: Evidence accumulates that *S. aureus* colonises 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 steroid insensitive 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 comorbidity 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 colonisation, 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 SNP, as well as the current lack of data concerning safety in longterm application of omalizumab has to be borne in mind and further studies have to be conducted.^[19]

Role of CMC Foam: Recurrence of sinonasal polyposis after endoscopic sinus surgery can be difficult to manage. Topical steroid sprays and irrigations may not provide adequate treatment and systematic steroid therapy is limited by side effects. Steroid infused carboxymethyl cellulose (CMC) foam as a treatment for recurrence of chronic rhinosinusitis with sinonasal polyposis after endoscopic sinus surgery has been tried. Four mL 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 finding in patients with recurrent sinonasal polyposis after endoscopic sinus surgery.^[20]

Role of Intranasal Furosemide: The best therapeutic approach to relapse of sinonasal polyposis is to interfere with the early phase on SNP development. A key element in this context is the oedematous infiltrate. Manipulation of this target may be effective in preventing relapses after surgery. According to this hypothesis, the genesis of oedema secondary to increase plasma and water absorption into the lamina propria of the NP tissue.^[21] The topical use of furosemide, a loop diuretic and inhibitor of the potassium

and sodium chloride co-transporter 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.^[22] 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.^[23] In the recent studies, furosemide is diluted in physiological solution (2 mL furosemide and 2 mL isotonic sodium chloride solution) administrated as nasal puffs (2 puffs per day per nostril, each puff corresponding to 50) for every alternate month for the first 2 years (total treatment, 4 months/year). After 5 years of treatment, furosemide was administrated 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 relapse, compared with 24.2% in the mometasone group and 30.0% in the untreated group.^[24] Also the severity of recurrence is much less. As there are no longterm 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 sinonasal polyposis, antifungal medical therapy has been an appealing and promising alternative in maintain treatment following FESS to reduce recurrence and its severity in polyposis patient.^[25,26] Amphotericin B is a natural polyene antifungal agent which binds to ergosterol, a component of cell wall of most fungi, leading to formation of ion channels and cell death; it may also act secondarily through oxidative damage to fungal cell membrane through creation of free radicals from its own oxidation.^[27] It is hypothesised that topical intranasal application of Amphotericin B can decrease the fungal load in sinonasal region, thereby decreasing the local eosinophilic inflammatory reaction to fungal antigens seen in many chronic rhinosinusitis with or without sinonasal polyposis patients.^[28,29] Amphotericin B is poorly absorbed through the gut when ingested orally, therefore there is little or no potential for systematic exposure to the drug when administered by the topical intranasal route.^[30] Direct mucoadministration 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.^[31] 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.^[28]

Role of Oral Antifungal: 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,^[32,33] though no single surgical technique has proved to be entirely curative and the recurrence rate is around 5-10%.^[33,34] Con-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 component 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.^[35,36] The use of CAS systems may allow for more precise dissections and greater rates of sinus patency outcomes and fewer complications.^[37] It is important postoperatively to regularly douche the nasal cavity with saline to prevent crusting and adhesions.^[38] Topical intranasal steroids are also a routine part of after surgery care to prevent recurrence.^[39]



Fig. 1



Fig. 2

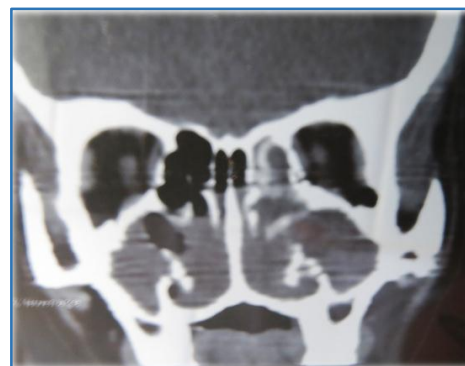


Fig. 3

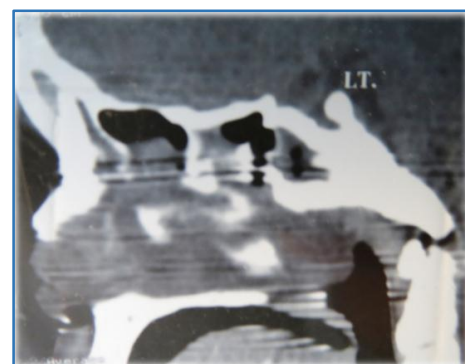


Fig. 4

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

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