

Update on Nasal Polyps: Etiopathogenesis

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Purpose of review: Nasal polyps is a common ENT disease with high medical failure and recurrence rate, reflecting unknown pathogenesis. The present review is an update on the etiopathogenesis of nasal polyps.

Recent finding: Several mechanisms have been proposed for the formation of nasal polyps, including allergy, mucosal allergy, autonomic imbalance, nitric oxide, superantigens, infection, abnormal transepithelial ion transport, mucopolysaccharide abnormality, mechanical obstruction and epithelial rupture. Eosinophils comprises more than 60% of the cell population. Activated T cells, mast cells and plasma cells are also increased compared with the normal nasal mucosa. The stroma has numerous mediators, including cytokines, growth factors, adhesion molecules, and immunoglobulins. Both Th1 and Th2 types of cytokines are upregulated independent of the atopic status. An increased production of GM-CSF, IL5, RANTES and eotaxin can contribute to chronic eosinophilic inflammation by regulating the migration, survival and activation of eosinophils.

Conclusion: Nasal polyps is a multifactorial disease, with infectious, noninfectious, inflammation, anatomic and genetic abnormalities. Chronic inflammation remains the central major factor in nasal polyps.

Keywords: Nasal polyps, Etiology, Pathogenesis, Histology

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Nasal polyps is a chronic inflammatory disease of the mucous membranes in nose and paranasal sinuses, and characterized by edematous masses of inflamed mucosa which forms a pedunculating mass with slim or broad base stalk. Most polyps originated from the clefts of osteomeatal complex⁽¹⁾ and extend into nasal cavity, leading to nasal obstruction, secretion, loss of smell, headache, and a reduced quality of life⁽²⁾. In the general population, the overall prevalence rate of nasal polyps in adults ranges from 1 to 4%⁽³⁾. The prevalence rate is much lower in children, except when associated with cystic fibrosis. With carefully endoscopic examination of cadavers, a quarter of individuals had polyps without a history of sinonasal disease⁽⁴⁾. Nasal polyps usually presents between the ages of 30 and 60 years. There is a strong male predominance, range between 2:1 and 4:1.

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Histology

Nasal polyps is characterized by massive tissue edema, resulting from a leakage of plasma through widened endothelial junctions of blood vessels. Based on histological findings, Hellquist HB.⁽⁵⁾ classified polyps into four types: (I) Eosinophilic edematous type (edematous stroma with a large number of eosinophils); (II) Chronic inflammatory or fibrotic type (large number of inflammatory cells mainly lymphocytes and neutrophils with fewer eosinophils); (III) Seromucinous gland type (Type I+ hyperplasia of seromucous glands); (IV) Atypical stromal type.

The general histopathological classification of nasal polyps is eosinophil- and neutrophil-dominated inflammation⁽⁶⁾. The more common histopathological type is eosinophil-dominated inflammation (63-95%)⁽⁷⁻¹⁰⁾. However, a study in Thailand reported a lower prevalence rate of eosinophil-dominated inflammation (Hellquist type I + type III = 17.9%)⁽¹¹⁾.

For practical reasons, Stammberger H⁽¹²⁾ classified nasal polyps into five groups, based on endoscopical and clinical criteria, their response to different therapy, association with other diseases as

well as light microscopic appearance: (I) Antrochoanal polyp; (II) Large isolated polyps; (III) Polyps associated with chronic rhinosinusitis (CRS), non-eosinophil dominated, non-related to hyper-reactive airway syndromes; (IV) Polyps associated with CRS, eosinophil-dominated; (V) Polyps associated with specific disease (Cystic fibrosis, non-invasive/ non-allergic fungal sinusitis, malignancy).

Etiopathogenesis

Nasal polyps is a multifactorial disease, with infectious, noninfectious inflammation, anatomic, and genetic abnormalities. Most theories consider polyps to be the ultimate manifestation of chronic inflammation; therefore, conditions leading to chronic inflammation in the nasal cavity can cause nasal polyps. Several conditions are associated with nasal polyps, e.g. allergic and nonallergic rhinitis, allergic fungal sinusitis, aspirin intolerance, asthma, Churg-Strauss syndrome (fever, asthma, eosinophilic vasculitis, granuloma), Cystic fibrosis, Primary ciliary dyskinesia, Kartagener syndrome (chronic rhinosinusitis, bronchiectasis, situs inversus), Young syndrome (sinopulmonary disease, azoospermia, nasal polyps). Several hypotheses have been proposed to explain the pathogenesis of nasal polyps as follows:

Allergy

Allergy has been implicated because of three factors: the majority of nasal polyps have eosinophilia; the association with asthma; and the nasal findings that may mimic allergic symptoms and signs. A clinically respiratory allergy, particularly to perennial airborne allergens, might play a relevant role in the pathogenesis of nasal polyposis, probably through the induction of a longlasting inflammation of the nasal

mucosa⁽¹³⁻¹⁵⁾. Most evidence suggests that polyps is associated more strongly with nonatopic disease than with atopic disease^(1,16,17). Caplin et al⁽¹⁸⁾ found only 0.5% of atopic patients have nasal polyps. This is also supported by an extensive study by Settupane GA (Table 1)⁽¹⁹⁾; however, a closer look at previous studies shows polyps patients have a somewhat higher prevalence of positive allergy skin test than the general population (Table 2)⁽²⁰⁾.

Mucosal allergy

It has been postulated that patients who have been found to be "nonatopic" by skin tests or serum specific IgE may have IgE mediated disease localized to the nose. Meta-analysis of nine studies found that 19% of the nasal polyps patients had specific IgE manifested nasal mucosal allergy but no systemic allergy⁽²¹⁾. Although mucosal allergy has been considered, most evidence points to nasal polyps as a manifestation of a systemic disease, characterized by an eosinophil-dominated inflammation not only in the localized area of polyps formation, but in the entire airways.

Table 1. Prevalence of nasal polyps in a normal population, allergic rhinitis, asthmatic adults and chronic rhinosinusitis⁽¹⁹⁾

	Prevalence (%)
Normal population	1
Allergic rhinitis	1-5
Asthmatic adults	7
- IgE-mediated	5
- Non-IgE-mediated	13
Chronic rhinosinusitis	2
- IgE-mediated	1
- Non-IgE-mediated	5

Table 2. Prevalence of positive allergy skin test in polyps and general population⁽²⁰⁾

	Subjects tested (N)	Allergy tests (N)	> 1 Positive test	> 2 Positive test	> 3 Positive test
Polyps subjects					
- Settupane & Chafee 1977	211	>5	56%		
- Drake-Lee et al 1984	200	9	44%		
- Small et al 1985	19	6	47%	42%	32%
- Keith et al 1995	87	10	52%	40%	28%
General populations					
- Gergen & Turkeltang 1991	16,204	8	20%		
- Barbee et al 1976	3,012	5	34%		
- Friedhoff et al 1981	115	7	24%		
- Hagy & Settupane 1969	1,243	5	31%		

Vasomotor imbalance

This theory is implied because the majority of nasal polyps patients are not atopic and no obvious allergen can be found^(1,16,17,19). Patients frequently have a prodromal period of rhinitis prior to occurrence of polyps. Nasal polyps often has a poor vascularization lacks vasoconstrictor innervation⁽²²⁾. The impaired vascular regulation and increased vascular permeability may cause edema and polyps formation.

Bernouilli phenomenon

The Bernouilli phenomenon results in a pressure drop next to a constriction. This sucks the mucosa of narrow site, e.g. early contact between opposing mucosal surfaces in to the nose⁽²²⁾. It appears that the negative pressure induces the inflamed mucosa to project into the nasal cavity resulting in polyp formation⁽²³⁾. If this were the only factor, the mucosa nearest the nasal valve would be polypoidal in normal nose.

Epithelial rupture theory

Rupture of epithelium of nasal mucosa from allergy or infection can lead to prolapse of the lamina propria mucosa, forming polyps. The defects possibly are enlarged by gravitational effects or venous drainage obstruction. However, a study using scanning and transmission electron microscopy showed that the polyps epithelium was well preserved and no epithelial defects could be demonstrated⁽²⁴⁾.

Aspirin intolerance.

Many concepts advanced to explain the pathogenesis of aspirin intolerance and the association with nasal polyps. A well known clinical entity, Samter's or ASA triad, which is the product of three conditions: asthma, aspirin sensitivity and nasal polyps. It is a distinct clinical syndrome, characterized by the precipitation of rhinitis and asthma attacks by aspirin and most of other nonsteroidal anti-inflammatory drugs (NSAIDs). Persistent rhinitis appears at an average age of 30 years, then asthma, aspirin intolerance, and nasal polyps⁽²⁵⁾. The cyclooxygenase (COX) response to ASA was selectively altered in patients with AIA. Altered COX1 or COX2 enzyme might be more vulnerable to ASA or could produce unknown metabolites that stimulate cysteinyl leukotriene (Cys-LT). Arachidonic acid metabolism is shunted into the highly inflammatory leukotriene pathway^(26,27). This leads to a decrease in the levels of PGE₂, the antiinflammatory PG. LTC₄ synthase overexpression further increases the number

of cysteinyl LTs, tilting the balance toward inflammation^(28,29). This can contribute to uncontrollable inflammatory response and chronic inflammation.

Cystic fibrosis

Cystic fibrosis is one of the most common autosomal recessive disorders of white populations. Cystic fibrosis is caused by mutations in a single gene on chromosome 7, name cystic fibrosis transmembrane regulator (CFTR)⁽³⁰⁾. This causes both absence of cyclic AMP-regulated chloride channel and abnormal regulation of sodium channel, resulting in chloride impermeability and increased sodium absorption^(31,32). The increased sodium absorption and decreased chloride secretion result in net movement of water in to cell and interstitial space, leading to water retention, polyps formation and dehydration of secretion. Defective CFTR protein migration may also cause secondary from chronic inflammation⁽³³⁾.

Nitric oxide

Nitric oxide is a free radical gas, generated from L-arginine by a family of enzymes, the nitric oxide synthases (NOSs)⁽³⁴⁾. Nitric oxide plays a major role in nonspecific immunoreactions, regulation of vascular of tone, host defense, and inflammation in a variety of tissues^(35,36). Free radicals are kept in balance by the antioxidant defense system superoxide dismutase (SOD), catalase and glutathione peroxidase. Although transient, free radicals can overwhelm natural antioxidant defenses, result in cell injury, tissue damage and chronic disease⁽³⁷⁾. Karlidag et al⁽³⁸⁾ reported an increase in levels of nitric oxide and decrease in scavenging enzyme (SOD) in nasal polyps patients compared to controls, suggesting the presence of free radical damage in nasal polyps. Exhaled nitric oxide can reflect eosinophilic airway inflammation⁽³⁹⁾.

Infection

The role of infection is thought to be important by some in the genesis of polyp formation. This is based on experimental models in which multiple epithelial disruptions with proliferating granulation tissue have been initiated by bacterial infection with *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Bacteroides fragilis* (all common pathogens in rhinosinusitis) or *Pseudomonas aeruginosa*, which is often found in cystic fibrosis^(40,41). The role of induced granulomatous polyps on nasal polyposis formation in human is still dubious and needs to be proven.

Superantigen hypothesis

Staphylococcus aureus is present in the mucin adjacent to nasal polyps in about 60 to 70% of cases of massive nasal polyposis⁽⁴²⁾. These organisms always produce toxins, Staphylococcus enterotoxins A (SEA), Staphylococcus enterotoxins B (SEB) and Toxic shock syndrome toxin-1 (TSST-1), which may act as superantigens, causing activation and clonal expansion of lymphocytes with specific V region in the lateral wall of the nose^(43,44). These activated lymphocytes produce both Th1 and Th2 cytokines (IFN- γ , IL-2, IL-4, IL-5), leading to chronic lymphocytic-eosinophilic mucosal disease^(43,45). Specific IgE antibodies to SEA and SEB were detected in 50% of nasal polyps tissue⁽⁴⁶⁾ and specific IgE antibodies in serum to Staphylococcal (SEB, TSST) were found in 78% of nasal polyps patient⁽⁴⁷⁾.

Fungal infection

Fungi are ubiquitous in a habitable environment. Inhaled fungal elements become entrapped in the sinonasal mucus, causing eosinophils to shift from respiratory mucosa into the lumen by a yet unknown mechanism. Eosinophils then cluster around and attack the fungal elements. During this process, they release toxic mediators resulting in secondary mucosal inflammation⁽⁴⁸⁻⁵⁰⁾. Fungal elements were found on histology in 82% of chronic rhinosinusitis patients undergoing sinus surgery⁽⁵¹⁾. 45% of nasal polyps patients were positive on skin prick test with mold extracts and 40% were positive to *C. albicans*. Only 11% of control subjects were positive on skin prick test with mold extracts⁽⁵²⁾. Using novel collection and culturing techniques, mucus specimens from 96% of chronic rhinosinusitis patients showed cultures positive for fungi, but specimens from healthy controls also demonstrated fungi in 100% of the specimens⁽⁵³⁾. These data showed a common microscopic fungal colonization of the nose and paranasal sinus. In addition, Weschta et al⁽⁵⁴⁾ reported that topical amphotericin B nasal spray is ineffective in the treatment of chronic rhinosinusitis with polyps. The assumption of fungal elements as essential causative agents of chronic rhinosinusitis with nasal polyps is doubtful.

Genetic predisposition

Genetic etiology is suspected in the development of nasal polyposis on the basis of familial aggregation. Cystic fibrosis is an autosomal recessive disease associated with mutations of CFTR gene within region q31 on the long arm of chromosome 7⁽³⁰⁻³²⁾.

Human leukocyte antigen-DR (HLA-DR) are expressed on the surfaces of the paranasal inflammatory cells in the paranasal mucosa and nasal polyps. People with HLA-DR7-DQA1*0202 and HLA-DQB1*0202 haplotypes had a two or three times higher odd ratios for developing of nasal polyps. Patients with Samter's triad carried this DR7 alleles significantly more often ($p < .001$)⁽⁵⁵⁾. A significant association was also seen with HLA-A74 and nasal polyps⁽⁵⁶⁾.

Cellular composition

In the majority of nasal polyps, eosinophils comprise more than 60% of the cell population, except in cystic fibrosis and primary ciliary dyskinesia. There is an increase in activated T cells with CD8+ T cells predominating over CD4+⁽⁵⁷⁾. Mast cells and plasma cells are also increased compared with normal nasal mucosa⁽⁵⁸⁾. Electron microscopic studies have shown marked and widespread mast cell degranulation in all polyps studied, and the degree of degranulation is greater than in allergic rhinitis^(59,60).

Chemical mediators

Besides increased inflammatory cell infiltration, increased expression and production of a variety of proinflammatory cytokines and chemokines have been reported in nasal polyps. Histamine are markedly increased in nasal polyps, exceeding levels of 4000 ng/ml⁽⁶¹⁾. Both Th1 and Th2 type cytokines are up-regulated in polyps tissue independent of the atopic status⁽⁵⁷⁾. An increased production of granulocyte/macrophage colony-stimulating factor⁽¹⁷⁾, IL-5, RANTES and eotaxin can contribute to eosinophil migration and survival^(62,63). 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. IgA and IgE are also increased in nasal polyps⁽⁴⁶⁾. 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-epithelialcell/fibroblast interactions can contribute to the persistent eosinophilic inflammation seen in polyps⁽⁴²⁾.

Conclusion

Nasal polyps is a multifactorial disease with several different etiological factors. No single etiological factor can explain the pathogenesis of nasal polyps. Most theories consider polyps to be the ultimate mani-

festation of chronic inflammation; therefore, conditions leading to chronic inflammation in the nasal cavity can lead to nasal polyps. Chronic persistent inflammation is undoubtedly a major factor irrespective of the etiology.

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พยาธิกำเนิดโรคริดสีดวงจมูก

วิรัช เกียรติศรีสกุล

ริดสีดวงจมูกเป็นโรคที่พบบ่อยในหู คอ จมูก สาเหตุของโรคยังไม่ทราบแน่ชัด ทำให้ผลการรักษาไม่ดีเท่าที่ควร อัตราล้มเหลวของการรักษาและการเกิดซ้ำสูง มีสมมุติฐานการเกิดหลายประการอันได้แก่ ภาวะภูมิแพ้ ภูมิแพ้เฉพาะที่เยื่อจมูก การอุดตันโพรงจมูกและโพรงอากาศข้างจมูก ความผิดปกติของระบบประสาทอัตโนมัติ ก๊าซไนตริกออกไซด์ ซูเปอร์แอนติเจน การติดเชื้อ ความผิดปกติของการส่งผ่านอิออนที่เซลล์เยื่อผิว ความผิดปกติของ mucopolysaccharide และเซลล์เยื่อผิวฉีกขาด ริดสีดวงจมูกประกอบด้วยเซลล์ชนิด *eosinophils* มากกว่า 60% และมี mediators ต่างๆมากมาย ได้แก่ cytokines, growth factors, adhesion molecules และ immunoglobulins ซึ่ง cytokines พบได้ทั้งชนิด Th1 และ Th2 โดยไม่สัมพันธ์กับภาวะภูมิแพ้ GM-CSF IL5, RANTES และ eotaxin ที่พบเพิ่มขึ้นในริดสีดวงจมูกจะส่งเสริมให้เกิดการอักเสบเรื้อรังชนิด *eosinophils* เด่น
