Epidemiology of Nasal Polyps

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Core Messages

- The prevalence of nasal polyps (NP) in the population has been grossly estimated as 1–4%.
- An association between NP and allergic rhinitis (AR) is weak, with NP prevalence in patients with AR estimated between 1.5 and 1.7% and this incidence approaches that of the general population.
- Large cohort studies have revealed a strong association between asthma and NP.
- The incidence of NP increases with age and is likely the greatest between 40 and 60 years of age.
- If NP are found in a child, a workup for cystic fibrosis should be conducted.
- Genetic inheritance has been proposed as a possible etiology of NP but remains unclear.
- Up to 50% of aspirin insensitive patients have NP and up to 36% of patients with NP may have some form of analgesic insensitivity.
- Allergic fungal rhinosinusitis is a known underlying pathophysiologic etiology in a subset of CRS patients and is strongly associated with NP.
- Ethnic and geographic variation has emerged as a potential modifier in NP pathophysiology.

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2.1 Introduction

Mounting evidence suggests that nasal polyposis (NP) is a clinical manifestation of multiple possibly coexisting immunologic pathways, and because this entity likely reflects an array of disease states, the epidemiology is difficult to characterize. Phenotypically, chronic rhinosinusitis (CRS) can be classified as either CRS without NP or CRS with NP. CRS without NP, in general, reflects TH1-mediated inflammation [45]. Idiopathic CRSwNP comprises the vast majority of cases of NP, and this term typically implies a clinical picture of *diffuse* sinonasal polyposis dominated by TH2-mediated (eosinophilic) responses, at least in western patients. In rare cases, a distinct genetic, immunologic, or metabolic defect has been associated with the development of diffuse NP, and these cases will be discussed below. Furthermore, CRS with NP must be differentiated from antrochoanal polyps, which account for only 5% of polyp cases [24]. Antrochoanal polyps are usually unilateral and solitary and most often arise from the maxillary sinus. This is a distinct disease process that often presents at a younger age compared to CRSwNP. In contrast to CRSwNP, antrochoanal polyps reveal lesser degrees

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of eosinophilia with a more normal appearing mucosal surface and basement membrane [31].

The prevalence of NP in the population has been grossly estimated as 1–4%, though supporting evidence for this finding is scarce [24]. Older reports have suggested a prevalence ranging from 0.2 [12] to 2.2% [16], and autopsy studies have reported an incidence of bilateral NP at 1.5 [43] to 2% [25]. Various comorbidities such as allergic rhinitis (AR), generalized atopic status, and asthma have all been proposed as factors in the genesis of NP. Yet the data for these associations have been the subject of on-going investigations and conflicting reports can be identified. Variations in prevalence have also been reported as a function of demographic factors, including age and gender. In addition, hereditary factors and ethnic variations exist and must be considered. The present chapter is dedicated to elucidating the epidemiology of CRS with NP in general, as well as in the context of comorbid disease states and known underlying pathophysiologic processes.

2.2 Allergy and Asthma

Classic teaching has implied that NP formation is a product of an allergic response (atopy) to inhalant allergens. Although this relationship seems intuitive, current data suggest that this association is weak. NP prevalence in patients with AR is estimated to be between 1.5 [40] and 1.7% [14], and this incidence approaches that of the general population as previously described.

Large cohort studies have revealed a strong association between asthma and NP while consistently challenging the relationship between atopy and NP. In one investigation of over 2,000 patients, Settipane reported that NP were more common in nonallergic asthmatics vs. allergic asthmatics (13 vs. 5%, $p<0.01$) [39]. These data were corroborated by Grigoeras et al. who analyzed 3,817 Greek patients with chronic rhinitis and asthma. Overall, the incidence of NP in this population was 4.2% and NP prevalence was the greatest in nonallergic asthmatics vs. allergic asthmatics (13 vs. 2.4%). There was an association between NP and perennial allergy as opposed to seasonal [14].

Other studies have examined as to how factors such as NP and atopy may correlate with CRS severity, as measured by CT scan. In a group of 193 CRS patients treated at a tertiary care center, statistical analysis revealed that atopy was significantly more prevalent in the CRS without NP subgroup (32.3%) compared to those with CRS with NP (27.5%). Although the mean Lund–Mackay score was slightly greater in atopics vs. nonatopics (14.2 vs. 12.3, $p=0.05$), significance was lost when the cohort was separated into those with and without NP. In contrast, increased radiologic severity was observed in the CRS with NP group. Overall, these data suggest that the presence of NP is unrelated to atopy and is a better predictor of advancing radiologic disease [35].

A similar study examined 106 patients from a tertiary care center of which 49% were atopic by skin endpoint titration. Overall, atopics and nonatopics exhibited no difference in the prevalence of NP (38 vs. 37%). Presence of asthma, however, was an independent predictor for the existence of NP, which was observed in 57.6% of asthmatics vs. 25% of nonasthmatics ($p=0.0015$). As with previous reports, Lund–Mackay score was the greatest in *nonatopic* asthmatics, followed by atopic asthmatics, and then nonasthmatics. As expected, the Lund–Mackay score was the greatest in the polyp group, but it is important to note that this association was found to be independent of atopic status. In summary, these data indicated that asthmatic patients are more likely to have polyps than nonasthmatics [32]. Furthermore, the presence of asthma and polyps were each significant predictors of disease severity as measured by Lund–Mackay score. In contrast, atopy appears unrelated (or perhaps weakly related) to either polyp growth or advancing severity of radiologic disease.

The pathophysiology of CRS with NP and asthma may reflect a similar chronic inflammatory response in the upper and lower airways, at least in a subset of patients. An abundance of eosinophils is typically seen in the polyp tissue of patients with CRS with NP, while this is not consistently observed in patients with CRS without NP [17]. The inflammatory cellular infiltrate in asthmatics is also composed of eosinophils, mast cells, and CD4+ T lymphocytes [42]. Bachert et al. has theorized that the relationship between severe CRS and asthma may be due to the production of inflammatory cytokines in airways which induce the upregulation of eosinophils, mast cells, and basophils by the bone marrow upregulation. These inflammatory cells then migrate to the airway mucosa resulting in a reactive inflammatory response leading to NP formation [6].

2.3 Gender and Age

It has been suggested that the incidence of NP increases with age [14, 39]. Settipane reported that NP frequency reaches a peak in patients who are 50 years and over [39]. Furthermore, he reports that asthmatics over 40 years of age are four times more likely to have NP than those under 40 (12.4 vs. 3.1%, $p<0.01$) [39]. Larsen et al. reported similar results in a uniform population of Danish patients. Of 252 patients, they observed NP most commonly in patients who were 40–60 years old. Additionally, patients over 80 years of age were unlikely to have NP. The mean age of diagnosis of NP was 51 in males and 49 in females. In sharp contrast, unilateral antrochoanal polyps were diagnosed at a much younger age: males 27 years, females 22 years [24].

The discovery of NP in children is extremely rare. The estimated incidence of NP in patients less than 16 years of age is 0.1 [39] to 0.216% [24]. In a study of 1,051 pediatric allergic patients, only one had NP [40]. If NP are found in a child, a workup for cystic fibrosis (CF) should be conducted.

As with age, the literature varies in relation to the impact of gender on the development of NP. In Settipane's review of 211 NP patients, there was an equal distribution of males and females, 50.2 vs. 49.8% respectively [40]. Data published more recently using the Danish National Health Care insurance system to identify patients treated for NP differ with this prior observation. In fact, this cohort exhibited an increased incidence of NP in males over 20 years as compared to age-matched females. The male:female ratio of patients with NP was 2.9 in ages 40–50 and maximal at 6.0 for patients between 80–89 years of age [24]. The incidence was the greatest in both males and females in the age range of 40–69 years. In this group, NP was present in 1.68 male and 0.82 female patients per thousand annually. It is important to note that data from this Danish initiated study represent a homogenous population of 252 NP patients culled from 5 years of retrospective data.

2.4 Genetics

Genetic inheritance has been proposed as a possible etiology of NP. Studies have suggested that up to 14% of patients with NP have a family history of NP [13]. Attempts to delineate a hereditary pathway using monozygotic twin studies have yielded mixed results. In a report of twins with steroid-dependent asthma, only one had bronchospastic aspirin intolerance and NP while the other did not manifest these phenotypic traits [38]. Further attempts have been made to show an association of NP in families. In a cohort of 174 NP patients, 25% had a first degree relative with polyps (parent, sibling, or child) [10]. Forty-four patients manifested Samter's triad (aspirin intolerance, asthma, and NP) and 36% of these patients had a first degree relative with NP. Furthermore, 32% (57) of the polyp patients had both NP and asthma of which 30% had a first degree relative with polyps. Though a genetic predisposition to form NP is likely a significant factor, there is no clear Mendelian inheritance pattern in the vast majority of NP cases, and a gene–environment interaction is likely at work.

There are various disorders that are genetically inherited in which the formation of NP is a disease characteristic. CF is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. The gene product of CFTR is a chloride ion channel primarily in the exocrine glands of the lungs, liver, pancreas, and intestines. Approximately, 20% of patients with CF have NP [39]. A diagnostic work-up for CF should be conducted in any patient under the age of 16 who presents with NP.

Primary ciliary dyskinesia (PCD), also known as Kartagener's syndrome, is characterized by CRS, bronchiectasis, and situs inversus (reversal of internal organs). Defects in the dynein arms of cilia are primarily responsible for the immotility seen on mucosal biopsy; however, radial spoke defects and microtubular transposition anomalies have been identified [41]. Ultimately, the frequency of ciliary beat is abnormal and uncoordinated. PCD has been seen in both men and women leading investigators to conclude that this is an autosomal recessive disorder. However, recent observations of a nonconsanguineous family with retinitis pigmentosa (RP) and PCD have suggested an X-linked inheritance pattern [29]. It is likely that there may be more than one mode of inheritance pattern for PCD as investigation into left-right axis deviations in vertebrates has shown an autosomal dominant, recessive, and X-linked pattern [9].

When initiating medical treatment for CRS in patients with either CF or PCD, culture-directed

therapy should be considered. CF patients have a high likelihood of *Pseudomonas aeruginosa* infection and antibiotic therapy should be tailored to this pathogen. CF patients are often treated with maintenance antibiotics directed against *P. aeruginosa* consisting of macrolides or fluoroquinolones. Therapy may be aerosolized to increase the concentration delivered to the tissues with a low toxicity profile [44].

Young's syndrome is another disorder characterized by recurrent sinopulmonary disease, obstructive azoospermia, and NP [15]. This disease differs from CF and PCD in that sweat chloride tests are normal, as is ciliary function demonstrated by normal sperm tails and tracheal biopsies. Spermatogenesis is normal and the azoospermia results from an excess of inspissated secretions in the epididymis [15, 37]. The prevalence of Young's syndrome remains unclear, but it has been suggested to be responsible for up to 7.4% of male infertility [39].

A systemic vasculitic disorder, Churg–Strauss syndrome (CSS) commonly presents with upper airway symptoms. Originally felt to be comprised of four hallmark characteristics, bronchial asthma, CRS, eosinophilic vasculitis, and granulomas [30], there is likely phenotypic variation to this syndrome. The American College of Rheumatology accepts six primary characteristics of CSS: asthma, eosinophilia >10%, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. To qualify for a diagnosis of CSS, four of the six criteria should be present, yielding a sensitivity of 85% and a specificity of 99.7% [27]. CSS is a systemic vasculitis of small to medium-sized vessels and is associated with AR and/or CRS with or without NP [2, 3]. The exact mechanism of CSS is unknown, but eosinophil activation likely plays a major role [2]. Otolaryngologic manifestations may consist of AR, CRS with or without NP, nasal crusting, otitis media, and rarely, sensorineural hearing loss and unilateral facial palsy [2]. NP is present in up to 60% of patients with CSS and is likely an indicator of early disease [3]. Corticosteroids are highly effective in treating patients with NP associated with CSS [3].

2.5 Aspirin Intolerance

NP are frequently observed in patients who are insensitive to aspirin (acetylsalicylic acid) or nonsteroidal antiinflammatory drugs. In this subset of patients, these medications induce an acute asthmatic response within 30–90 min of ingestion [36]. This "triad" of symptoms, (bronchial asthma, CRS with NP, and aspirin insensitivity) is often referred to as Samter's triad or ASA-triad. In a majority of affected patients, aspirin challenges produce an acute bronchial response with rhinorrhea and nasal obstruction [33]. Aspirin insensitivity that causes urticaria without bronchospasm has not been associated with NP. It has been estimated that up to 50% of aspirin insensitive patients have NP and that 36% of patients with NP may have some form of analgesic insensitivity [39]. However, while considering all the patients undergoing endoscopic sinus surgery (ESS), including CRS with and without NP, approximately 4.6% had ASA-triad [19].

The development of a fully realized ASA-triad likely occurs over time. Initially, patients may present with chronic rhinitis. Within 5–10 years, aspirin-induced asthma will become apparent. Shortly thereafter, NP becomes prominent [34]. Nonallergic rhinitis with eosinophilia syndrome (NARES) has been proposed as a precursor in the pathway leading to ASA-triad [28]. It has been shown that NP epithelial cells from ASA-triad patients have abnormalities in basal and aspirin-induced generation of eicosanoids (products derived from arachidonic acid metabolism including prostaglandins, thromboxanes, and leukotrienes), ultimately leading to aspirin sensitivity [21].

NP of ASA-triad patients likely represent a unique phenotype of severe inflammation, which is more recalcitrant to both medical and surgical intervention. The NP of ASA-triad patients demonstrate increased edema and inflammatory infiltrate compared to the NP of aspirin tolerant patients [7]. Additionally, ASA-triad patients' response to surgery is universally poor, undergoing approximately ten times as many ESS procedures as that of ASA tolerant patients [19]. Furthermore, ASA-triad patients have a significantly higher rate of symptom recurrence (nasal obstruction, facial pain, postnasal drip, and anosmia), regrowth of NP at 6-month follow up [7, 19], and lack of statistical improvement in FEV1 [7].

2.6 Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a known underlying pathophysiologic etiology in a subset of CRS patients and is strongly associated with NP. Classically, a diagnosis

of AFRS is made when the following five hallmark characteristics are present: a type I hypersensitivity to *dematiaceous* fungi, NP, paranasal CT scan findings of inspissated mucus with calcification, eosinophilic mucus containing Charcot-Leyden crystals without fungal invasion into the surrounding sinus mucosa, and positive fungal stains from sinus contents [8, 22]. Intraoperatively, the eosinophilic mucus is inspissated, tan colored with a thick sticky consistency. Rarely does a patient with suspected AFRS satisfy all five of these criteria. However, the diagnosis can be made based on clinical suspicion and intraoperative observations of eosinophilic mucus and NP. Staining for fungal elements in intraoperative biopsies has proven to be inconsistent even in patients who are strongly suspected of having AFRS.

The incidence of AFRS has not been well established, but patient characteristics likely influence disease manifestation. Approximately 5–10% of CRS with NP patients have AFRS [8, 11]. This is typically a disease of younger adults, with a mean age of diagnosis between 22 [26] and 28 years of age [46], which is significantly lesser than that observed in non-AFRS patients. Studies have suggested that there is an increased prevalence of AFRS in southern, more humid climates. Recent reports have suggested that lower socioeconomic status may also play a role. In patients treated at a tertiary medical center in South Carolina, a significant proportion of the AFRS patients (24.1%) were uninsured or Medicaid recipients as opposed to 5.2% of the non-AFRS CRS with NP group. Furthermore, a significant portion of the AFRS group was African American (61.1%) who resided in counties with a greater African American population and more advanced poverty status [46]. These data raise the point that although AFRS may be more prevalent in various ethnic groups, socioeconomic status may also be a factor in that African Americans accounted for a significant portion of the un- or underinsured. It may be possible that lower socioeconomic status and thus, lack of access to health care, may have allowed for disease progression in this series.

2.7 Ethnicity and Geography

As the exact mechanism of NP formation remains a topic of investigation, ethnic and geographic variation has emerged as a potential modifier in the pathophysiology. In a Caucasian population, NP have been shown to have a strong eosinophilic component, likely due to the upregulation of interleukin (IL)-5 [4]. In addition to increased IL-5, eotaxin and eosinophilic cationic protein (ECP) are significantly elevated in NP homogenates and indicate amplified eosinophilic inflammation [45]. Additionally, transforming growth factor (TGF) β1, a cytokine known to stimulate the extracellular matrix and inhibit IL-5 synthesis [1], is downregulated in NP [45]. Therefore, a cytokine cascade culminating in the overproduction of IL-5, with downregulation of TGF-β1, may potentiate the eosinophilic response and have deleterious effects on the extracellular matrix simultaneously [45]. Of note, these results originate from a population of Caucasian patients from the country of Belgium.

Interestingly, this increase in eosinophils in NP is not consistent across various ethnicities. NP in Asian countries show a neutrophilic pattern rather than the previously discussed eosinophilic [18]. Yet, the clinical manifestation of NP remains similar between Asians and Caucasians. Zhang et al. attempted to further characterize the variations seen in Asian polyps. Polyp tissue samples from 27 Chinese patients from the Guangdong province of China were harvested. As with similarly affected Caucasian patients, most of the Asian patients had been treated with nasal steroids and antibiotics. Some had received Chinese herbal medicines. The samples were compared to a group of matched Caucasian Belgian patients, where Chinese polyps had a significantly lower incidence of eosinophils ($p < 0.01$) [47]. A Korean cohort has shown a similar preponderance of noneosinophilic NP [20]. In this study of 30 NP patients, not only were 66.7% noneosinophilic, but the basement membrane thickness of the polyps was found to be significantly thinner in the noneosinophilic vs. eosinophilic group (8.2 ± 3.5 vs. 13.9 ± 4.5 μm) [20].

Though the predominant inflammatory cellular infiltrate differs between Caucasians and Asians, commonalities are also apparent. Zhang et al. [47] reported that ten of the Asian polyps contained IgE against *Staphylococcus aureus* enterotoxins (SAE), which is consistent with the previously reported data that one-third of Caucasians with NP and asthma have IgE to SAE [5]. As in white subjects, tissue IgE and sIL-2R are elevated in Asian polyps. Eosinophilic infiltrate is decreased in Asian polyps as measured by ECP and IL-5/eotaxin levels compared to the tissue from

Caucasians. Total IgE was elevated in allergic NP compared with nonallergics, but ECP was not increased. Thus allergic disease likely has a negligible impact on ECP levels and eosinophil recruitment. Similar findings have been made in Caucasian polyps [5, 32, 35]. TGF-β1 was significantly downregulated in Asian polyps compared with inferior turbinate controls. Furthermore, TGF-β1 was extremely low in the NP groups with IgE to SAE suggesting a modulatory effect of staphylococcal enterotoxins. This finding has previously been observed in Caucasians. Of the Asian group, only two had asthma and nine were allergics. There was no difference between the allergics and nonallergics in relation to eosinophilic infiltrate.

It is clear that variation in the physiology of NP differs amongst Asians and Caucasians, yet there have been only limited investigations into other ethnic and racial backgrounds. A collaboration between three otolaryngology departments from various continents, Eritrea (Africa), China (Asia), and Switzerland (Europe) attempted to better characterize the racial variation of NP [23]. In this report, the African and Chinese participants did not receive preoperative steroids or antibiotics whereas the Caucasians were treated preoperatively with prednisolone 1 mg/kg/day for 5 days as well as trimethoprim/sulfamethoxazole for 10 days. Compared to Chinese and Caucasians, Africans presented with more progressive disease in which NP extended into the nasal cavity and were ulcerated. Eosinophil density was also greater in African polyps ($p<0.001$) compared to Chinese and Caucasian NP. There was no difference in the amount of eosinophils between Chinese and Caucasian NP. Plasmocytes and lymphocytes were abundant in Chinese and Caucasian NP and rare in African NP. No difference was observed in the number of mast cells in any group. Unfortunately, the patients included in these analyses were not standardized in relation to preoperative treatment. The Caucasian cohort had been treated with preoperative steroids which would likely suppress the presence of inflammatory mediators in the polyp biopsies. Both the Chinese and African cohorts received no preoperative treatment. The root cause of these discrepancies is likely due to socioeconomic disparities among the study countries resulting in a significant variation in the patients' access to health care and likely affected the molecular data. Just as NP of Caucasians and Asians can exhibit significant cellular and molecular differences, it is possible that polyps from African patients also show significant variation in cellular and molecular profile.

Take Home Pearls

- NP is a phenotypic manifestation of multiple possible immunologic processes.
- The significant association between NP and asthma suggests similar underlying pathophysiology that is independent of atopy.
- Although some CRS with NP cases are associated with established genetic syndromes, most patients likely have multiple, subtle, and as yet unknown genetic variations that combine with environmental factors resulting in polyp formation.
- Further study is necessary to elucidate the key factors that account for the variability in polyp epidemiology.

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