

Chronic rhinosinusitis with nasal polyps in the elderly: Assessing current evidence

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ABSTRACT

Background: The recently reported prevalence of chronic rhinosinusitis (CRS) among people >60 years old was 4.7%, with CRS emerging as the sixth most common chronic condition in the elderly. There is still a dearth of studies that focused on older patients, however, regarding the characteristics of CRS with nasal polyps (CRSwNP).

Objective: The emerging role of CRSwNP endotyping to enable a tailored medical approach (for elderly patients also) was investigated.

Method: The present review of data reported predominantly in the past 5 years aimed to critically discuss the pathophysiologic, clinical, and prognostic features of CRSwNP in elderly patients.

Results: Although the existing data were not final, they supported the notion that geriatric patients can be managed safely by adopting the same surgical algorithm as for younger adults, including endoscopic sinus surgery (ESS). As for medical therapies, prolonged systemic steroid treatment for CRSwNP should be given with caution to elderly patients because they risk significant adverse effects. There is increasing evidence of a lower CRSwNP recurrence rate after ESS in the elderly than in young adult patients. Contrary to findings in younger patients, recently, analysis of preliminary data showed that histologically eosinophilic CRSwNP or high blood eosinophil counts were not significantly associated with a higher recurrence rate in elderly patients.

Conclusion: A great challenge in the field of geriatric CRSwNP is to investigate the different endotypes in large series (also by means of biomarker assay in blood and polyp tissue) to identify rational and tailored diagnostic, therapeutic (medical and/or surgical), and follow-up modalities.

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Based on the Medical Expenditure Panel Survey for 2007, which concerned 225.1 million Americans, Bhattacharyya^{1,2} estimated the prevalence of chronic rhinosinusitis (CRS) (with nasal polyps [CRSwNP] or without nasal polyps [CRSsNP]) at $4.9 \pm 0.2\%$, or 490/10,000 population.³ When analyzing the information obtained on 57,128 people ages 15–75 years who lived in 19 centers in 12 European countries, the Global Allergy and Asthma Network of Excellence study concluded that the overall prevalence of CRS, based on European position paper on rhinosinusitis and nasal polyps (EP³OS) criteria, was 10.9% (range, 6.9–27.1%).⁴

The size of the geriatric population is on the increase in developed countries: the U.S. Census Bureau estimated that 20% of the U.S. population will be at least 65 years old by 2030.⁵ Recently, the prevalence of CRS

among people >60 years was calculated at 4.7%,^{6,7} and rhinosinusitis was judged to be the sixth most common chronic condition in the elderly.⁸ When considering electronic health records (for 2001–2010) from 446,480 Geisinger Clinic primary care patients, Tan *et al.*⁹ found that CRS was diagnosed in 1364 elderly patients (ages >65 years): CRSsNP in 1231 patients, and CRSwNP in 133 patients. In focusing on data reported in the past 5 years, the aim of the present review was to critically discuss the pathophysiologic, clinical, and prognostic features of CRSwNP in elderly patients, and also to examine the emerging role of CRSwNP endotyping for the purpose of providing a tailored precision treatment for this age group as well as for younger patients.

PATHOPHYSIOLOGY OF CRSwNP IN THE ELDERLY

There are several factors that predispose the elderly to chronic paranasal sinus inflammatory disease. Age-related changes in the nasal and paranasal mucosa include (1) an increase in the volume and a decrease in the elasticity of the nasal mucosa; (2) a reduced or absent nasal cycle, partly due to a declining ciliary efficacy; (3) atrophy of the supporting fibrofatty tissues of the nose, with a potential loss of support for the nasal structures (narrowing of the nasal valve), which

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gives rise to more nasal obstruction; (4) a higher incidence of rhinorrhea with more mucus due to increased glandular activity and more viscous secretions; and (5) excess mucus crusting.^{10–12}

In the natural history of CRS, Cho *et al.*¹³ indicated that an impaired epithelial barrier function might become worse with aging, whereas eosinophilic inflammation could wane. Cho *et al.*¹⁴ stated that S100 proteins were reduced in patients with CRS; in particular, S100A8/A9, which is important in epithelial barrier function, was particularly decreased in elderly patients with CRS. S100A8/A9 has antimicrobial activity against *Staphylococcus aureus*, *Klebsiella* species, and fungi.¹³ Cho *et al.*¹⁴ found, in association with a significant age-related decline in S100A8/A9, an increase of insoluble gp130 (sgp130) in nasal tissue samples from patients with CRSwNP, although there was no age-related difference in interleukin (IL) 6/soluble IL-6 receptor production. The expression of the S100A8/A9 gene and protein was increased significantly by IL-6/soluble IL-6 receptor plus tumor necrosis factor α in normal human bronchial epithelial cells: this increase was blocked by sgp130.

Cho *et al.*¹⁴ concluded that their results support the hypothesis that increased sgp130 in older patients might inhibit IL-6 *trans*-signaling, impair barrier function, and decrease S100A8/A9 production in elderly patients with CRSwNP. A better understanding of immunosenescence has shed light on changes that occur with aging in both the innate and the adaptive immune systems. There are changes in antigen presentation that lead to a weaker response of specific antibodies. A decrease in total immunoglobulin E levels, and a diminished response of the eosinophils to stimulation by cytokines with aging have also been demonstrated.¹⁰ Aging in patients with CRS is also characterized by an increasing likelihood of comorbid conditions and the use of several types of medication, such as bisphosphonates, non-steroidal anti-inflammatory drugs, antihypertensive agents, antidepressants, and vitamins.¹⁵

PATHOLOGIC AND LABORATORY FEATURES OF CRSwNP IN THE ELDERLY

In Western countries, CRSwNP is associated with type 2 inflammation and eosinophilia of the nasal polyps, whereas mixed inflammatory patterns are identified in Asian patients with CRSwNP.¹⁶ In a study on 349 patients with CRSwNP (enrolled in 2001, 2006, and 2011), Shin *et al.*¹⁷ concluded that the prevalence of eosinophilic nasal polyps has continued to increase in Korea and that the pattern of this sinonasal disease was becoming similar to the picture seen in Western countries. Eosinophilic and noneosinophilic polyps are claimed to histopathologically be two entities with distinct genetic and protein expression patterns.¹⁸

Ample evidence has been collected of an association between the histologic evidence of polyps with a rich eosinophilic component and a higher disease recurrence rate after endoscopic sinus surgery (ESS).^{19–23} Brescia *et al.*¹⁵ recently reported finding no difference in the distribution of cases of CRSwNP with eosinophilic or noneosinophilic histologic types in the two age groups they considered (*i.e.*, >65 years old versus 20–40 years old). When Kim *et al.*²⁴ analyzed 63 Korean patients with CRSsNP and 70 with CRSwNP, they found that elderly patients with noneosinophilic nasal polyps had a lower neutrophilic infiltration and a lower expression of neutrophil-associated cytokines than younger patients with the same condition. The investigators reported that these findings correlated with a better postoperative course in the older patients.

Cellular proliferation and angiogenesis are associated with the pathophysiology of nasal polyps. Shin *et al.*²⁵ conducted an immunohistochemical analysis on 20 patients with CRSwNP, divided into two groups by age (20–30 years versus ≥ 65 years old). They found a significantly lower expression of proliferating cell nuclear antigen and Ki67 in the polyps of the geriatric patients than in those of the young adults, whereas the expression of vascular endothelial growth factor did not differ between the two groups. However, Ottaviano *et al.*²⁶ reported a trend toward a statistically significant inverse association between the intensity of endoglin, which is a component of the receptor complex of transforming growth factor β (a pleiotropic cytokine that modulates angiogenesis), and the patient's age (<65 versus ≥ 65 years old) at the time of surgery for CRSwNP.

Few clinical studies have been conducted on the role of blood sampling in establishing the features of CRSwNP. High eosinophil levels in peripheral blood have been examined as a potential predictor of a histologic diagnosis of eosinophilic CRSwNP.^{27,28} A direct association between CRSwNP recurrence rates and blood hypereosinophilia was first reported by Ikeda *et al.*,²⁹ then confirmed by Tokunaga *et al.*³⁰ Recent studies of ours also found a direct association between CRSwNP recurrence rates and blood basophil levels.^{31,32} In a series of 43 consecutive elderly patients with CRSwNP, however, laboratory findings revealed no association between CRSwNP recurrences and blood eosinophil counts or percentages, or blood basophil counts or percentages.¹⁵ A preliminary retrospective investigation on 39 elderly patients with CRSwNP found that the mean neutrophil-to-lymphocyte ratio, eosinophil-to-lymphocyte ratio, and basophil-to-lymphocyte ratio did not differ significantly between the groups of patients with and without recurrent polypoidosis.³³

The differences in terms of pathophysiology contributing factors and laboratory and pathologic parameters

Table 1 Distribution of the elderly (≥ 65 years old) and young adult (20–40 years old) patients with CRSwNP by main pathophysiology contributing factors, and laboratory, pathologic, and prognostic variables*

Variables	Elderly Group (<i>n</i> = 43)	Young Adult Group (<i>n</i> = 71)	<i>p</i> Value
Allergy, no. (%)	8 (18.6)	31 (43.7)	<0.05
Asthma, no. (%)	12 (27.9)	16 (22.5)	n.s.
Aspirin-exacerbated respiratory disease, no. (%)	3 (6.9)	7 (9.8)	n.s.
Blood eosinophil count, mean $\pm$ SD, cells $\times 10^9$ /L	0.3 $\pm$ 0.2	0.4 $\pm$ 0.5	n.s.
Blood basophil count, mean $\pm$ SD, cells $\times 10^9$ /L	0.03 $\pm$ 0.01	0.03 $\pm$ 0.02	n.s.
Polyposis histology, patients with eosinophilic CRSwNP, no. (%)	16 (37.2)	27 (38.0)	n.s.
Recurrence rate, no. (%)	5 (11.6)	20 (28.2)	0.05

CRSwNP = Chronic rhinosinusitis with nasal polyps; n.s. = not significant; SD = standard deviation.

*According to Ref. 15.

in elderly patients (≥ 65 years old) versus young adults (20–40 years old) with CRSwNP as found by Brescia *et al.*¹⁵ are summarized Table 1.

CRSwNP PROGNOSIS IN ELDERLY PATIENTS AFTER SURGERY

In a prospective setting, when considering the three age groups of patients with CRSwNP, classified as pediatric (5–18 years old), adult (19–65 years old), and geriatric (> 65 years old), Lee and Lee³⁴ found that the patient's age influenced the objective postoperative outcome, which was worse in the pediatric patients and better in the geriatric patients. They hypothesized that a more limited mucosal regeneration and cellular proliferation with aging might contribute to a lower incidence of scarring or meatal narrowing after surgery. Shin *et al.*²⁵ compared objective surgical outcomes by using endoscopic scores in 20 patients with CRSwNP divided into two age groups (20–30 years and ≥ 65 years of age): although the scores did not differ to a statistically significant degree between the two groups, the geriatric group had better scores than the young adult group.

An investigation on 179 consecutive patients who underwent ESS for CRSwNP concluded that the discriminatory power, in terms of disease recurrence, of a three-variable panel (age < 65 years, serum basophil percentage, and eosinophilic type) coincided with an area under the curve (receiver operating characteristic) of 0.7028, which is an acceptable discriminatory power according to the Hosmer-Lemeshow scale.^{31,35} In a sample of 43 consecutive elderly patients and 71 consecutive young adult patients with CRSwNP, Brescia *et al.*¹⁵ found that the disease recurred after surgery less often in the elderly (Table 1). Their results also revealed significant associations in the elderly group between CRSwNP recurrence and allergy, CRSwNP re-

currence and asthma, and CRSwNP recurrence and aspirin-exacerbated respiratory disease but not between CRSwNP recurrence and eosinophilic CRSwNP histology.

FUNCTIONAL RESULTS AFTER SURGERY FOR CRSwNP: QUALITY OF LIFE IN THE ELDERLY

The 20-item Sino-Nasal Outcome Test was used by Colclasure *et al.*⁸ to assess elderly patients before surgery and then at 3, 6, and 12 months after ESS. They found the symptom improvement in their geriatric population comparable with that of other age groups.⁸ When considering subjective surgical outcomes in 20 elderly patients who underwent ESS for CRSwNP, Lee and Lee³⁴ also reported that the following symptoms listed in the questionnaire had improved significantly vis-à-vis the preoperative situation: nasal obstruction, purulent discharge, postnasal drip, headache, facial pain or discomfort, or foul odor, with the exception of olfactory impairment.

Several studies demonstrated that the performance of the olfactory system diminishes in the geriatric population.¹⁰ Loss of smell is often one of the main symptoms reported by non-elderly and elderly patients with CRSwNP. The limited series by Lee and Lee³⁴ of elderly patients who underwent ESS for CRSwNP showed no significant improvement of preoperative olfactory impairment. When considering three subcohorts of patients with CRSwNP divided according to age (ages 18–39 versus 40–59 versus ≥ 60 years), Busaba³⁶ nevertheless, found that 71% of the elderly patients reported an improvement in dysosmia after surgery, the young adult subcohort reported a significantly higher rate of improvement in olfactory function.

ENDOTYPING CRSwNP IN GERIATRIC PATIENTS

CRSwNP is just one phenotype of CRS, and the clinical phenotypes are unable to provide a full picture of all the pathophysiologic cellular and molecular mechanisms that underlie this condition.^{37,38} A better understanding of the diversity of CRS has led to the identification of disease variants as different endotypes. Current interest in CRS endotyping stems from earlier research efforts in the sphere of asthma, which is a similarly heterogeneous inflammatory disorder that affects the epithelium of the lower airways.³⁹

After a retrospective chart review of 390 patients with CRS examined at the Northwestern University, Cho *et al.*¹⁴ found that elderly patients (>60 years) with CRS had a higher prevalence of nasal polyps and asthma than did the younger patients. However, after comparing two cohorts of patients with CRSwNP (>65 years old versus 20–40 years old), Brescia *et al.*¹⁵ reported that there was no significant difference between the two groups in the distribution of asthma. Interestingly, there is emerging evidence of asthma in older adults being phenotypically distinct from the condition seen in younger patients.⁴⁰ The impact of the aging process on the immunologic pathways that underpin asthma in the aging lung is still not clear, and epigenetic, environmental, and/or microbiologic triggers might be involved.¹⁵

CONCLUSION

Topical and short-term oral steroids show significant benefit on nasal symptoms, nasal polyp size, and nasal airflow also in elderly patients with CRSwNP. No serious adverse effects of topical nasal steroids (fluticasone propionate, beclomethasone dipropionate, mometasone furoate, budesonide, flunisolide) have been reported.³ As concerns medical therapies, prolonged systemic steroid treatments for CRSwNP obviously need to be administered with caution and monitored in elderly patients because of the risk of significant adverse effects (*e.g.*, adrenal failure, osteoporosis, diabetes mellitus, cataract, glaucoma, hypertension, psychosis, skin bruising, muscle weakness, gastritis, peptic ulcer).⁴¹

Several studies demonstrated that leukotriene receptor antagonists, *e.g.*, montelukast, are well tolerated at all ages, including the elderly patient.^{41,42} If the medical treatment failed, although we still lacked robust data in this area, it seemed that elderly patients can be safely managed in the same way as younger adults as regards ESS for CRSwNP. There is increasing evidence of a lower recurrence rate after ESS for CRSwNP in the elderly patient than in young adult patients. Further investigations on larger, prospective series are mandatory to confirm that strict postoperative follow-up and

adjuvant postoperative medical treatment (in particular, oral steroid courses) may not be necessary in the case of elderly patients.

Contrary to reports on several consecutive series of adults with CRSwNP, analysis of recent preliminary data indicated that histologic evidence of polyps rich in eosinophils or high blood eosinophil counts were not significantly associated with higher recurrence rates in elderly patients with CRSwNP. Immune-mediated diseases may be influenced by aging, and, in the pathogenesis and development of CRSwNP, the role and biologic activity of eosinophils may change over time.

Recent literature has strongly supported the hypothesis that asthma in older adults is phenotypically distinct from the condition seen in younger patients. In the field of geriatric CRSwNP, too, a great challenge lies in investigating the different endotypes in large series (also by means of biomarker assays in blood^{43,44} and polyp tissue) to establish rational and tailored diagnostic, therapeutic (medical and/or surgical), and follow-up modalities for this disorder.

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