International Journal of Otolaryngology Sciences

ISSN Print: 2664-9225
ISSN Online: 2664-9233
Impact Factor: RJIF 5.44
IJOS 2023; 5(1): 01-08
www.otolaryngologyjournals.com
Received: 05-01-2023
Accepted: 12-02-2023

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Medical condition: Persistent rhinosinusitis accompanied by nasal polyps and asthma

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DOI: https://doi.org/10.33545/26649225.2023.v5.i1a.7

Abstract
Individuals diagnosed with persistent rhinosinusitis accompanied with polyps in the nasal cavity, which is distinguished by the presence of a type 2 immunological signature, frequently experience severe and recurring symptoms. Lower respiratory tract disorders, such as asthma, frequently coexist with other medical illnesses and have comparable underlying physiological mechanisms. Chronic rhinosinusitis with nasal polyps (CRSwNP) accompanied with asthma is distinguished by the presence of eosinophilic infiltration in the affected tissues and elevated levels of immunoglobulin E (IgE) in the immediate environment. From a clinical perspective, the presence of concomitant asthma in individuals with chronic rhinosinusitis with nasal polyps (CRSwNP) is linked to heightened sinonasal symptoms and a worse quality of life. Furthermore, managing this condition by medicinal and surgical interventions poses greater challenges. The coexistence of nasal polyposis with asthma presents challenges in terms of disease management. This comorbidity is associated with higher susceptibility to exacerbations, heightened airway obstruction, and a greater extent of Eosinophilic inflammation. Individuals diagnosed with chronic rhinosinusitis with nasal polyps (CRSwNP) who also have concurrent aspirin-exacerbated respiratory disease (AERD) are a subgroup characterized by the presence of very severe and challenging-to-manage symptoms. Moreover, these patients typically exhibit a high degree of nasal polyp severity. The diagnosis and treatment of respiratory co-morbidities can be greatly aided by the identification and understanding of shared pathophysiology pathways in the lower as well as the upper airways. The compelling justification for developing systemic medicines that precisely target prevalent type 2 inflammatory mechanisms is the systemic inflammatory link that exists among rhinosinusitis that is chronic with polyps in the nasal passages (CRSwNP) and asthma.

Keywords: Asthmatic, rhinosinusitis, inflammation, polyps, comorbidity

Introduction
Chronic rhinosinusitis is collection of conditions characterised by inflammatory processes of the sinonasal mucosa. The aetiology of CRS is multifaceted, encompassing several components such as immunological and epithelial barrier mechanisms, which are impacted by variables such as the microbiome, environmental factors, and genetic factors. The prevalence of this condition ranges from around 9.7% to 12.4% among the European populace at large and the US [1]. The illness exhibits heterogeneity in both its clinical manifestations and inflammatory characteristics. In a general sense, chronic rhinosinusitis (CRS) may be categorised into two primary phenotypes. Chronic rhinosinusitis with nasal polyps (CRSwNP), including around 18% to 20% of all instances of rhinosinusitis which is chronic (CRS), is considered the most incapacitating of the two phenotypes. This condition is correlated with increased morbidity and has the potential to impact the respiratory health of adult individuals with lower airway illness. The estimated prevalence of chronic rhinosinusitis with nasal polyps (CRSwNP) is around 1.1% in the United States, while in Europe, estimates range between 2.1% and 4.4% [2, 3].There is substantial evidence from epidemiological, clinical, and pathophysiology investigations indicating a strong association and frequent coexistence between combined symptoms of chronic rhinosinusitis, nasal polyps, and asthma (CRSwNP). Strong association (P .01) between proinflammatory identities of nasal and bronchial samples from individuals who suffered from chronic rhinosinusitis with polyps in the nasal cavity (CRSwNP) demonstrates intimate relationship between the nasal mucous membrane and lower airway inflammation.

This finding provides additional evidence to support the existing concept of interconnected airways in patients who have asthma and coexisting allergic rhinitis. Individuals with severe asthma have further data establishing the link connecting inflammatory processes within the sinonasal as well as lower airways. A significant favourable link has been shown regarding the intensity of sinusitis illnesses, as assessed by the degree of mucosal thickness observed on CT scans as well and the frequency of inflammation of the airways. The identification of white blood cells in bronchial phlegm or blood from the peripheral region, as well as the measurement of nitric oxide concentrations in air that is exhaled is used to assess inflammation [4]. Patients diagnosed with persistent rhinosinusitis with polyps in the nasal cavity (CRSwNP) and concurrent asthma exhibit a more pronounced manifestation of the condition. This is seen by a greater likelihood of experiencing recurring nasal polyps (NP) and a higher dependency on corticosteroid treatment, in comparison to patients only diagnosed with asthma (4% against 1% of patients, respectively) [5]. The coexistence of nasal polyposis with asthma poses additional challenges in terms of disease management. Studies have indicated that this combination is associated with increased difficulty in controlling asthma symptoms, heightened susceptibility to exacerbations [6].

A well-documented manifestation of chronic rhinosinusitis with nasal polyposis (CRSwNP), frequently observed alongside asthma, is referred to as AERD (Figure 1).The demographic of interest include those aged 19 to 25 years. The primary clinical features are prolonged rhinosinusitis with polyps in the nasal passages, allergies and asthma, and increased vulnerability to COX-1 inhibiting agents [7]. The main aim of research is to understand the same physiopathological mechanics behind persistent rhinosinusitis with polyps in the nasal cavity (CRSwNP), a disorder impacting the upper respiratory tract, and asthma, a condition mostly affecting the lower respiratory tract. Following this, the investigation will examine the implications of these mutual processes on the co-occurrence of many medical conditions, the intensity of the ailment, as well as the overall well-being and satisfaction with life. Subsequently, we shall elucidate the pathophysiological mechanisms behind AERD and explore the potential for treating CRSwNP and AERD as a unified condition, owing to their overlapping clinical features.

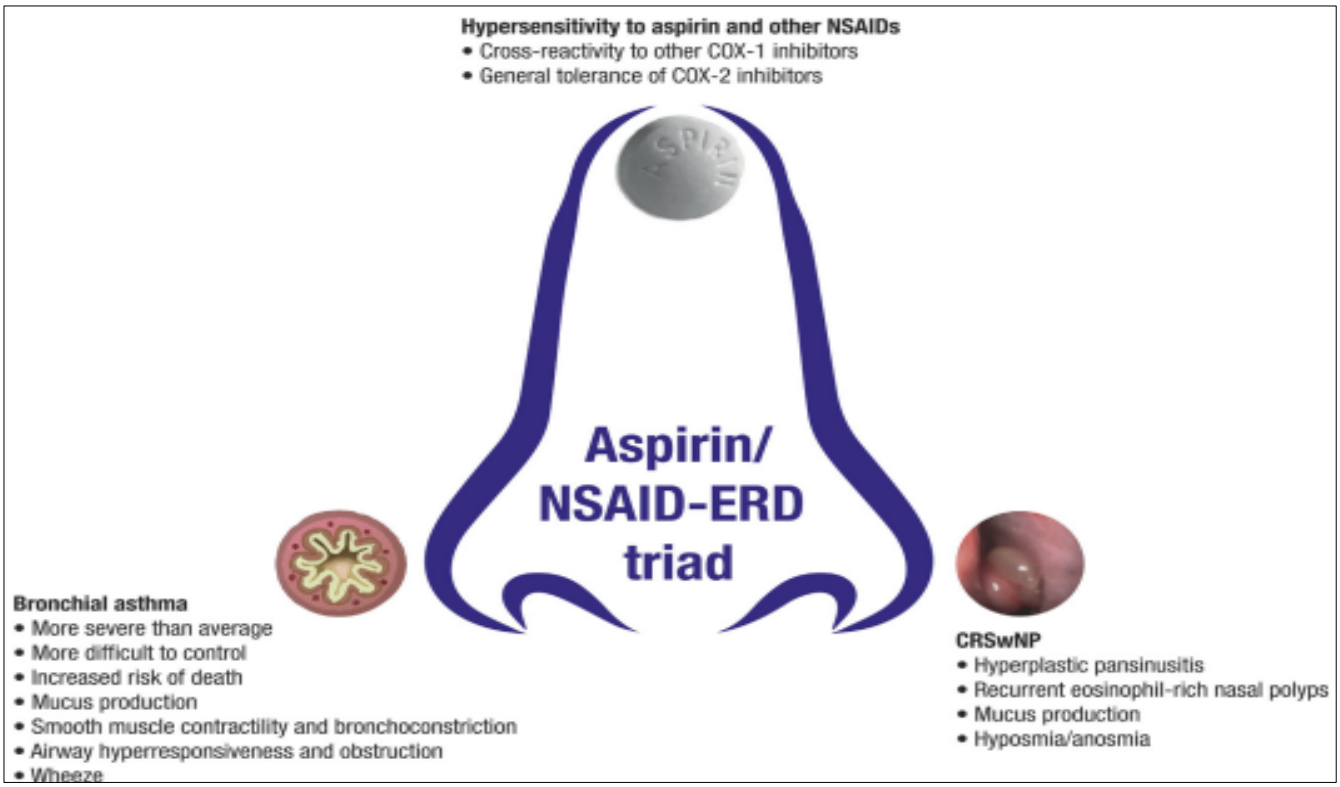

Fig 1: Clinical characteristics of the aspirin/NSAID-ERD traid. COX, Cyclooxygenase; CRSwNP, chroic rhinosinusitis with nasal polyps; NSAID, Nonsteroidal anti-inflammatory drug; NSAID-ERD, NSAID-exacerbated respiratory disease. Figure adapted with permission from Kowalski and bavbek [19]. Copyright © 2020 European academy of allergy and clinical immunology. All rights reserved.

The Coexistence and Severity of CRSwNP and Asthma

The results of an extensive epidemiological study carried out by the GA2 LEN demonstrate a strong and consistent association between asthma and chronic rhinosinusitis (CRS) [8]. Similarly, research has demonstrated a strong association between asthma and CRS w NP. Studies indicate that the prevalence of comorbid asthma in people with CRSwNP ranges from 40% to 67%, with estimations showing that up to 67% of individuals with CRSwNP also have asthma. The numerical value provided is 4.8. Furthermore, it is worth noting that a significant number of individuals with CRSwNP frequently have undetected asthma. Ragab *et al.* [9] discovered in their investigation that a considerable fraction of individuals identified as having chronic rhinosinusitis with nasal polyps (CRSwNP) possessed indications of lower airway engagement. In their study, the researchers found that a significant proportion of those included in their sample, namely 60%, shown lower airway involvement. Among these patients, 24% were diagnosed with asthma, while 36% exhibited symptoms indicative of small airway sickness. In the assessment of bronchial hyper responsiveness in individuals diagnosed

with chronic rhinosinusitis with nasal polyps, it was determined that a notable proportion, ranging from 28% to 40%, had asthma that had not been previously recognized [10]. CRSwNP has a tendency to be correlated with the manifestation of asthma in adults, either in the form of early-onset asthma occurring between the ages of 18 and 39, or late-onset asthma occurring after the age of 40. However, it is often not connected with childhood asthma. On the other hand, this has been associated with the development of asthma throughout childhood (before the age of 16) as well as the start of asthma in early adulthood (before the age of 40 [11]. Moreover, it is worth noting that CRSwNP has a higher prevalence among individuals with severe allergic reactions (57.1%-62% of patients) compared to those with moderate asthma (37%-43.9% of patients). This observation implies that the coexistence of CRSwNP and asthma may potentially contribute to the severity of asthma symptoms [12]. The incidence of CRSwNP and its coexistence with asthma tends to rise in correlation with advancing age, suggesting that the overall burden of both conditions is expected to escalate within an ageing demographic [13]. Patients diagnosed with asthma who also have concomitant CRSwNP exhibit elevated levels of inflammation in the lower airways and experience poorer management of their asthma symptoms compared to those without CRSwNP. Additionally, these patients with asthma and CRSwNP demonstrate higher levels of eosinophils in their sputum and experience reduced lung function when compared to patients diagnosed with CRSsNP [14].

CRSwNP Pathophysiology

From a pathophysiological perspective, CRSwNP is showcased by a prevailing type 2 inflammatory response. This type 2 inflammatory environment within the nasal polyps not only contributes to the persistent inflammatory condition of the mucous membranes in the nasal and sinus cavities, but also plays a role in the structural changes and proliferation of the nasal polyps. In Caucasian populations, chronic rhinosinusitis with nasal polyps (CRSwNP) is frequently characterized by a type 2 inflammatory signature, observed in around 80% of cases. Conversely, Asian people with either CRSwNP tend to exhibit an alternative inflammatory profile, which is mostly driven by T helper (Th) 1 and/or Th17 cells [15, 16]. The presence of type 2 inflammation in CRSwNP is characterized by a substantial rise of the concentrations of important cytokines, chemokines associated with type 2 immune response, and eosinophils when compared to individuals without the condition [17]. Furthermore, it has been shown that individuals with CRSwNP have increased amounts of ILC2, macrophages, and mast cells in nasal polyp biopsies [18, 19]. The process of nasal polyp (NP) development entails the temporal interplay between components immunity, both naturally occurring and adaptive, as well as the restructuring of the nasal mucosa. This restructuring is marked by alterations in epithelial cells, epithelial-mesenchymal transition, an increase in goblet cells, degradation of the extracellular matrix, deposition of fibrin, and the occurrence of tissue edema [20]. The presence of abnormalities in the sinonasal epithelial barrier has been detected in individuals with CRSwNP, specifically characterized by a decrease in the expression of proteins involved in cell adhesion and tight junctions [18]. After being injured by infectious agents, proteases, or allergens, the damaged epithelium shows a response by activating Th2-promoting cytokines such IL-25, IL-33, and TSLP [21]. Among these factors, thymic stromal lymphopoietin (TSLP) has the highest level of induction and possesses the ability to stimulate type 2 innate lymphoid cells (ILC2s) and mast cells, leading to the secretion of type 2 cytokines, particularly IL-5 and IL-13. Consequently, TSLP plays a crucial role in enhancing the kind 2 inflammatory reaction [21]. According to *in vitro* studies, it has been observed that the cytokines IL-4 and IL-13, which belong to type 2 cytokines, have the potential to sustain barrier dysfunction along with the type 2 immune response. This is achieved by the stimulation of TSLP expression [22]. People who have nasal polyps with a diagnosis of chronic rhinosinusitis (CRSwNP), the interplay between the host and the environment at the mucosal lining of the sinonasal region is compromised as a result of several causes (such as decreased epithelial barrier function, disruption of the microbiome equilibrium, and failure of the mucociliary apparatus). This impairment subsequently gives rise to immune system dysfunction and the persistence of inflammatory processes. Epithelial barrier dysfunction further facilitates pathogen encroachment that may trigger off immune responses, hence intensifying inflammation. As an illustration, a prior investigation documented that 63% of individuals diagnosed with CRSwNP exhibited colonisation by Staphylococcus aureus. This bacterium has been demonstrated to release enterotoxins that can stimulate the synthesis of antigen-specific immunoglobulin E (IgE), hence enhancing type 2 inflammatory reactions [16].

The Pathophysiological Connection between CRSwNP & Asthma

Both are characterised by impaired epithelial barrier function and have a common type 2 immunopathology. The presence of concomitant asthma in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) has been shown to result in an increase in the expression within the upper as well as the lower airways, and the release of immunological mediators mediated by IgE producing type 2 cytokines. This finding is seen in Figure 2 [23]. Patients diagnosed with chronic rhinosinusitis with nasal polyps (CRSwNP) who have a type 2 immune response, characterised by the presence of immunoglobulin E (IgE), eosinophils, interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-5 (IL-5), frequently experience more severe manifestations of the disease. These individuals are prone to greater polyp prevalence and are more likely to develop asthma that is challenging to manage well [24]. CRSwNP in individual's alongwith asthma is distinguished by the presence of tissue eosinophilia and elevated levels of local immunoglobulin E (IgE). Furthermore, research done on Japanese patients has demonstrated a notable correlation between concomitant lower airway illness and eosinophilic subtypes of CRS, both with and without nasal polyps (NP) [25]. Moreover, the presence of an association between tissue eosinophilia and olfactory dysfunction in chronic rhinosinusitis with nasal polyps (CRSwNP) implies that eosinophils or the cytokines they produce might lead to partial (hyposmia) or complete (anosmia) loss of the sense of smell, which is a prevalent symptom of CRS [26]. Asthma and chronic rhinosinusitis with nasal polyps (CRSwNP), in addition to other type 2 inflammatory illnesses such atopic dermatitis (AD) and eosinophilic esophagitis (EoE), exhibit common

immunological and histological characteristics marked by the presence of type 2 inflammatory cytokines [21].

The Aetiology and Pathophysiology of Aspirin-Exacerbated Respiratory Disease (AERD)

Often, Aspirin-Exacerbated Respiratory illness (AERD) manifests abruptly during early adulthood, exhibiting a characteristic progression of symptoms. The illness course often starts with the emergence of chronic rhinitis/rhinosinusitis, followed by the advent of asthma, and culminating in COX-1 inhibitor-induced responses. Allergic eosinophilic rhinosinusitis (AERD) in conjunction with nasal polyps (NP) often becomes clinically apparent around the mid-30s, with a mean age of onset at 34 years. This condition is frequently associated with severe asthma symptoms and nasal polyps [27]. Aberrations in the production, metabolism, and expression of leukotrienes and arachidonic acids biosynthetic enzymatic agents as well as the presence of regulators like cysteinyl steroid hormones and PGs, which are prostaglandins [28]. Arachidonic acid is released from cellular membrane phospholipids in cell membranes of mammals upon activation of phospholipase A2. Eicosanoids are synthesised from arachidonic acid after it is converted by COX enzymes and lipoxygenase pathways. These eicosanoids serve as signalling molecules, including prostaglandins, thromboxanes, leukotrienes, and lipoxins, which play crucial roles in various cellular activities. The insufficient regulation of COX-2 has been widely hypothesised to play a role in the development of AERD. This is supported by the observation that the expression of COX-2 mRNA in nasal polyps (NP) from AERD patients is much reduced compared to polyps from those who have asthma/rhinitis who do not have adverse reactions to aspirin, while the expression of COX-1 mRNA remains unaffected [29]. Previous studies have indicated that modifications in the process of eicosanoid metabolism may take place regardless of an individual's susceptibility to aspirin, and these identified modifications are associated with the extent of eosinophilic inflammation [30]. A research conducted *in vitro*, it was observed that changes in the COX pathway were linked to the development of nasal polyps (NP) in individuals, regardless of whether they had aspirin-exacerbated respiratory disease (AERD) or not. When stimulated with IL-1b, fibroblasts formed by people suffering from asthma who are either tolerant or intolerant to aspirin demonstrated a significant reduction in PGE2 production and did not exhibit any upregulation of COX-1, COX-2, or EP2 (a receptor for PGE2), when compared to fibroblasts obtained from the mucous membrane of the nose of control individuals. The authors hypothesized that a decrease in the production of prostaglandin E2 (PGE2) may play a role in the development of neuropathic pain (NP), as it reduces the anti-inflammatory and tissue-repairing effects of PGE2. Additionally, they suggested that dysregulation of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) may be a contributing factor in the susceptibility of certain individuals with asthma to experiencing worsened symptoms when exposed to nonsteroidal anti-inflammatory drugs (NSAIDs). The significance of the innate immune response in aspirin-exacerbated respiratory disease (AERD) is becoming more evident. The pathogenesis of Aspirin-Exacerbated Respiratory Disease (AERD) is profoundly influenced by the dysregulation of immunological responses mediated by thymic stromal lymphopoietin (TSLP). The numerical value 69. In addition, the pathogenesis of Aspirin-Exacerbated Respiratory Disease (AERD) involves the activation of mast cells through an innate type 2 response, which is primarily mediated by the overproduction of cysteinyl leukotrienes and the elevated expression of IL-33 in the nasal polyps of AERD patients. These factors significantly contribute to the development and progression of AERD. These mechanisms have the capacity to induce eosinophilic inflammation, activate mast cells, and stimulate IgE production independently [31].

The activation of the mitogen-activated protein (MAP)-kinase pathway and the translocation of nuclear factors are believed to have a significant impact, recognising the p38 MAP-kinase pathway as the principal signalling mechanism at play [32]. It has been suggested that there is a reduced ability of IL-1β to generate COX-2 [33].

CRSwNP with comorbid AERD

The prevalence of AERD among individuals diagnosed with CRSwNP has been reported to range from 8% to 26%. The meta-analysis revealed that the prevalence of Aspirin-Exacerbated Respiratory Disease (AERD) was around 7% among all individuals diagnosed with asthma, with a twofold increase observed in those with severe asthma. It has been shown that a significant majority, over 90%, of individuals diagnosed with CRSwNP and AERD have severe nasal polyps. Individuals aged 76 and patients diagnosed with CRSwNP and concurrent AERD have been recognised as having the most severe and challenging-to-manage condition. Individuals diagnosed with CRSwNP who also have AERD typically have a younger age demographic and a greater likelihood of experiencing recurrent symptoms following surgical intervention, in comparison to CRSwNP patients who are tolerant to aspirin. In a retrospective cross-sectional research conducted in the United States, a total of 1393 individuals diagnosed with CRSwNP were examined. The study revealed that CRSwNP tends to manifest as a more severe condition in women compared to males. Additionally, it was seen that women had a higher likelihood of experiencing concomitant asthma ($p<.001$) and aspirin-exacerbated respiratory disease (AERD) ($p<.05$) in conjunction with CRSwNP [34]. CRSwNP in individuals diagnosed with AERD is characterised by notably pronounced accumulation of eosinophils in the affected tissues, along with a heightened presence of type 2 inflammation and elevated levels of interleukin-4 (IL-4). Elevated levels of IFN- γ mRNA transcripts and heightened IL-4 expression have been seen in the nasal polyps (NP) of individuals diagnosed with chronic rhinosinusitis with nasal polyps (CRSwNP) and concurrent aspirin-exacerbated respiratory disease (AERD), in comparison to the NP of CRSwNP patients who are tolerant to aspirin and those without any health conditions (healthy controls) [35]. Interleukin-4 (IL-4) and interferon-gamma (IFN-γ) have been observed to upregulate the expression of leukotriene C4 synthase. Additionally, these cytokines have been detected on mast cells and eosinophils, indicating that Aspirin-Exacerbated Respiratory Disease (AERD) is characterized by a combination of Th1 and Th2 immune responses.The presence of concomitant asthma and/or AERD in individuals with CRSwNP has been demonstrated to have a notable adverse effect on physical well-being when compared to CRSwNP in isolation [36]. A comparative analysis was conducted on individuals

diagnosed with asthma and chronic rhinosinusitis (CRS), specifically distinguishing between CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). The findings revealed that patients with both asthma and CRSwNP had the most elevated scores on the 22-item Sino-Nasal Outcome Test, particularly in relation to diminished olfactory or gustatory perception and face discomfort or pressure [37]. Furthermore, it was observed that those diagnosed with CRSwNP, both with and not with asthma, as well as those with CRSwNP and AERD, showed the worst overall health survey results (36-item Short Form)(SF-36). This outcome suggests a lower quality of life in terms of health-related quality of life (HRQoL) for individuals with CRSwNP and AERD. The average SF-36 scores of patients with CRSwNP were found to be significantly lower when compared to the population norms that were adjusted for age.

Patients diagnosed with CRSwNP have a higher likelihood of encountering anosmia, or a diminished sense of smell, when they concurrently suffer from asthma as a comorbidity [38]. In the GA2 LEN study, a significantly higher correlation was seen between asthma and chronic rhinosinusitis (CRS) accompanied with an olfactory deficiency, which is a symptom strongly linked to nasal polyps (odds ratio [OR]: 4.25; 95% confidence interval [CI]: 3.74-4.71) compared to the correlation between COPD and CRS without olfactory impairment. Furthermore, it is noteworthy that the extent of olfactory impairment is considerably more pronounced in individuals diagnosed with AERD when compared to patients with aspirin-tolerant CRSwNP. It is worth mentioning that the olfactory deficiency serves as a factor that correlates for the result of oral aspirin challenge [39].

Table 1: The epidemiological and pathophysiological links between upper and lower airway diseases and possible targeted treatment options.

	Incidence (%)*	Endotype	Disease onset/mean age of onset	Severity/impact on QoL	Approved biologic therapy?
CRS	10.9[]	Mixed/heterogeneous[]		++	No
CRSwNP	2–4[8]	Type 2	Adult (42 years)	++	Yes
CRSwNP + asthma	40–67[†9,27]	Type 2	Adult or late adult onset	+++	Yes, in uncontrolled CRSwNP and severe asthma
CRSwNP + AERD	8–26[†20,23]	Type 2	Late adult onset	+++++	Only for AERD + severe asthma or uncontrolled CRSwNP
Asthma	7.9–12[99,100]	50% type 2	Childhood	+++	Only for CRS + severe asthma
Asthma + CRSwNP	7[†101]	Predominantly type 2	Late adult onset	++++	Only for NP + severe asthma

The Shared Pathophysiology of Chronic Rhinosinusitis with Nasal Polyps and Asthma/Aspirin-Exacerbated Respiratory Disease: Implications

The same pathophysiological mechanisms observed in airways have significant repercussions of detection and treatment of respiratory comorbidities. It is common in clinical practise to see both the lungs and the nose as distinct entities. In contemporary medical practice, it is considered advantageous to employ a comprehensive diagnostic strategy that involves the identification of specific endotypes for both asthma and CRSwNP. As previously mentioned, a significant number of individuals suffering from severe asthma exhibit concomitant CRSwNP. There is an increasing agreement among the medical community that addressing CRSwNP is crucial in order to enhance and optimize asthma management [40]. Initial therapy for the condition often involve the use of topical corticosteroids, nasal saline irrigation, and in certain cases, particular antibiotics such as doxycycline. The use of intranasal corticosteroids has been found to be effective in reducing the size of nasal polyps, alleviating sino nasal symptoms, and enhancing the quality of life for patients. Conversely, oral corticosteroids have demonstrated the ability to decrease polyp size and improve symptoms, however they may be associated with significant systemic adverse effects [41]. Sino nasal surgery may be required in cases when medicinal therapy are ineffective or when substantial sino nasal illness is present. Functional endoscopic sinus surgery (FESS) has been shown to have the potential to enhance clear evidence of sinus infection on CT scans and relief from symptoms related to the nose. However, it is important to note that nasal polyps (NP) may still reoccur even after undergoing surgery [42]. Previous studies have demonstrated that individuals diagnosed with both CRSwNP and asthma tend to undergo a greater number of sinus operations compared to those with CRSwNP alone. Furthermore, it has been observed that patients with aspirin-exacerbated respiratory disease (AERD) often require a higher frequency of sinus surgeries in comparison to CRSwNP patients who are tolerant to aspirin [43]. The approach to managing CRSwNP in patients with AERD is comparable to that in people without hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs).

There exists a pressing imperative to enhance the degree of control over chronic rhinosinusitis with nasal polyps (CRSwNP) and attain heightened levels of patient satisfaction and prevention of disease. There is a pressing need for targeted therapeutics (as indicated in Table I) that may effectively impede type II inflammation frequently observed in these disorders. Ideally, a singular therapeutic approach should be developed to address the pathological conditions affecting both the airways, while simultaneously mitigating the hypersensitivity associated with nonsteroidal anti-inflammatory drugs (NSAIDs). The emergence of biological medicines that specifically target variables linked to type 2 inflammation has led to a notable increase in the range of possible treatments available for chronic rhinosinusitis with nasal polyps (CRSwNP) in recent years. Dupilumab, an entirely human monoclonal antibody targeting the IL-4Rα receptor, is now the sole biologic agent

authorised by both the United States FDA for use as an adjunctive maintenance therapy in adult individuals with inadequately managed CRSwNP [44].

The therapy of dupilumab, which involves the simultaneous suppression of IL-4 and IL-13 activity, has been found to have extensive effectiveness in managing both upper and lower airway diseases, as well as atopic dermatitis (AD) and eosinophilic esophagitis (EoE) [45]. In the subgroup analyses conducted on individuals with AERD from two extensive phase 3 studies on chronic rhinosinusitis with nasal polyps (CRSwNP), it was observed that the administration of dupilumab resulted in significant enhancements compared to a placebo in various measures related to the upper and lower airways over a span of 24 weeks. These improvements included a decrease in opacification observed in sinus CT scans, reduction in polyp size, and amelioration of symptoms associated with CRS such as nasal congestion and olfactory function. Additionally, there was an enhancement in the forced expiratory volume in 1 second and a decrease in the 6-item Asthma Control Questionnaire score [46, 47]. In recent studies, many biologics have demonstrated efficacy in lowering the size of nasal polyps, alleviating nasal congestion, and ameliorating other symptoms often associated with chronic rhinosinusitis with nasal polyps (CRSwNP). The aforementioned treatments encompass the fully humanized anti-IgE monoclonal antibody known as omalizumab, which has received approval from the FDA for its efficacy in managing allergies. Analysis conducted on combined data from two phase 3 clinical trials investigating the effects of omalizumab, significant reductions in congestion of the nasal cavity as well as polyp size were reported after a 24-week treatment period in patients with AERD as well as those without AERD [48]. There is an expectation that focused biological agents might potentially provide more pronounced therapeutic outcomes in those who have both asthma and CRSwNP, in addition to in those who have the additional comorbidity of AERD [49].

Conclusion

Lower respiratory tract illnesses, such as asthma and AERD, frequently coexist with CRSwNP and have similar underlying mechanisms. Chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma exhibit variability in the underlying inflammatory mechanisms, characterised by either type 2 or, less frequently, non-type 2 inflammatory patterns. On the other hand, aspirin-exacerbated respiratory disease (AERD) is especially characterised by a type II inflammatory profile. Patients diagnosed with CRSwNP who have a type 2 immunological profile frequently experience severe and recurring symptoms, as well as concurrent lower airway complications. CRSwNP accompanied by respiratory comorbidities such as asthma and AERD exhibits a heightened manifestation of sinonasal symptoms, particularly nasal congestion and olfactory impairment, as well as a diminished quality of life (QoL). Moreover, the management of this condition poses greater challenges in terms of both pharmacological and surgical interventions. However, it is noteworthy that in routine clinical practise, the nasal cavity and the pulmonary system tends to be regarded as distinct entities. As our comprehension pertaining to the pathophysiology simultaneous, persistent upper and lower airway disorders expands, the justification for focused treatment that tackles the fundamental immunological pathways of both conditions becomes increasingly compelling. The association between CRSwNP and asthma, in terms of systemic inflammation, presents a strong justification for implementing systemic therapy strategies that target the fundamental inflammatory mechanisms in individuals affected by both illnesses. This technique would enable the implementation of a standardised therapy regimen for individuals presenting with CRSwNP and concurrent asthma.

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How to Cite This Article
George S, Thamarassery U. Medical condition: persistent rhinosinusitis accompanied by nasal polyps and asthma. International Journal of Otolaryngology Sciences. 2023; 5(1): 01-08.