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LITERATURE REVIEW

Rhino-bronchial syndrome: A complex and interdisciplinary entity from the otorhinolaryngology perspective

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ABSTRACT

The rhino-bronchial syndrome is a condition characterised by chronic rhinosinusal inflammation and simultaneous chronic pulmonary pathology (asthma, chronic obstructive pulmonary disease, chronic bronchitis). The most prominent link is between sinonasal pathology, specifically allergic rhinitis, and asthma, characterized by increased eosinophil infiltration in both the nasal and bronchial mucosa, independently of the level of allergen exposure. Chronic rhinosinusitis, especially when associated with nasal polyps, can be an important risk factor for asthmatic patients and vice-versa.

The patients with rhino-bronchial syndrome need a multidisciplinary approach by a medical team: otorhinolaryngologist, pneumologist and allergologist.

KEYWORDS: rhino-bronchial syndrome, asthma, allergic rhinitis, rhinosinusitis, multidisciplinary approach.

INTRODUCTION

The interdisciplinary group of the Italian ENT Society (SIO) and the Interdisciplinary Association for the Study of Respiratory Diseases (AIMAR) elaborated in 2003 the Consensus Report on the Rhino-Bronchial Syndrome, defining the rhino-bronchial syndrome (RBS) as a "nosologic entity that develops when a hyper-reactive process, a recurrent or chronic inflammation of the upper airways, or anatomical alterations of the rhinosinusal district facilitate the development of an inflammatory state (of infectious or immunological origin), in the lower airways, also compromising their function"[1].

Over the years, there were many researchers sustaining the idea that the upper and the lower airways diseases are generated by the same inflammatory process[2-4]. The entire respiratory pathway presents an anatomical continuity and shares the same pathophysiological mechanism.

Diseases such as rhinitis, rhinosinusitis, allergy, asthma seem to present similar symptoms and appear to be related to one another[4,5]. As a result, the rhino-bronchial syndrome includes complicated rhinosinusitis and bronchitis with productive cough, asthma, allergies, but also cases of primary ciliary dyskinesia, cystic fibrosis or immunoglobulin deficiency. All these aspects sustain the concept of unified airway disease[4-6].

PATHOGENESIS OF RHINO-BRONCHIAL SYNDROME

From the pathophysiological point of view, there are different theories which try to explain the link between upper and lower airways.

Nasobronchial reflex

The nasobronchial reflex is responsible for laryngospasm, bronchoconstriction and respiratory

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suppression while diving[7,8]. The efferent pathways of the vagus nerve, with origin connection with the trigeminal nerve, are responsible for the contraction of bronchial muscles[9]. Triggers irritating the nasal mucosa (e.g., allergens, harmful substances), following the above-mentioned mechanism, can initiate the nasobronchial reflex, inducing bronchoconstriction, increase airways resistance and cessation of respiration during expiration.

The role of the nasobronchial reflex in the development of RBS is still controversial[10]. In the literature, there are supporting and opposing views on this subject. Studies performed on both animal subjects and humans have shown increased pulmonary resistance after stimulation of the nasal mucosa[11-15]. Corren et al.[15] demonstrated the role of allergen exposure in altering bronchial responsiveness in patients with allergic rhinitis. On the other hand, there are studies which present no significant changes in lung resistance or no notable decrease in flow rates after nasal mucosa stimulation with different irritants[16-18].

Inflammation mechanisms

Any type of inflammation of the upper respiratory tract is able to extend and produce an inflammatory reaction at the lower respiratory tract level. The systematic inflammatory response is involved in this propagation due to the inflammatory mediators released in the systemic circulation (e.g., eotaxin, cytokines, interleukins, eosinophils)[2,6,8,19].

Pharyngobronchial reflex

Bronchoconstriction initiated by irritation of the hypopharynx with postnasal secretion can explain the pharyngobronchial reflex[2-4].

RHINITIS AND BRONCHOPULMONARY DISEASES

Inflammation of the inferior turbinates, regardless of cause, can contribute to lower airways diseases. Over the years, many studies have demonstrated the relationship between rhinitis and asthma on epidemiologic and pathophysiologic level[2,8,20-22]. There is evidence of cross-talk between the upper and lower airway compartments, demonstrated by the fact that allergic or non-allergic irritation at one level induces an inflammatory reaction both locally and in the other respiratory level[23,24].

Epidemiologic data shows that up to 40% of patients with allergic rhinitis (AR) also have asthma, and 94% of patients diagnosed with allergic asthma also have allergic rhinitis[20]. In a meta-analysis published in 2019, Shen et al.[22] reported a prevalence of AR with asthma between 6.69% and 14.35% and an association of asthma with AR between 26.67% and 54% among the Chinese population. As a consequence, the World Health Organisation, through the Allergic Rhinitis and its Impact on Asthma (ARIA) program, has made efforts to evaluate risks, educate and implement evidence-based therapeutic plans for both allergic rhinitis and asthma all over the world[25].

Several authors have evaluated the pathophysiologic relationship between rhinitis and asthma by analysing mucosal inflammatory markers after nasal provocation tests[2,15,18,21,26]. They showed that nasal allergen challenge can increase bronchial reactivity, induce bronchial inflammation, and, viceversa, the bronchial endoscopic challenge with allergens triggers a nasal inflammatory reaction. It can be said that there is a "bidirectional" relationship between nasal and bronchial inflammation. An IgE-mediated inflammatory reaction is triggered in both the nasal mucosa and the bronchi. As a result, inflammatory mediators such as cytokines, histamine and leukotrienes are released into the systemic circulation[20,27]. Studies have shown the implication of bone marrow in the allergic-type inflammation[27]. An increase in IL-5 (interleukin-5) produces T-cells in the bone marrow, inducing the differentiation of eosinophil and basophil progenitors, which are then released into the peripheral blood, subsequently increasing their concentration in the upper and lower airways. Eosinophil accumulation generates a release of cytokines responsible for edema and inflammation. These reactions lead to epithelial damage which is repaired via increased cell proliferation.

The similarity between the inflammation type of the upper and lower respiratory tracts is sustained by biopsy samples extracted from the nasal mucosa and the bronchia[28-30]. Crimi et al.[31] demonstrated the same bronchial inflammatory response following allergen-specific stimulation in patients suffering from both asthma and rhinitis.

A correlation was identified between nasal and bronchial inflammation in patients diagnosed with chronic obstructive pulmonary disease (COPD), sustained by elevated IL-8 concentration compared to controls[32].

The link between non-allergic rhinitis and asthma seems to be due to the lower airways hyperresponsiveness[2,20,21,27].

POSTNASAL DRIP AND BRONCHOPULMONARY DISEASES

Postnasal drip is considered a common symptom in allergies (the so-called allergic postnasal drip), rhinosinusitis and the flu, and it is also known as

upper airway cough syndrome. It occurs when excessive mucus is produced by the nasal and sinus mucosa and drips down ~~on~~ the back of the throat[2,3].

The gastroesophageal reflux disease (GERD) has also been linked to the development of postnasal drip syndrome, such as pregnancy, certain foods and nasal irritants (chemicals, perfumes, smoke, cleaning products).

Usually, when awake, retronasal secretions are swallowed and the cough reflex prevents the secretion from flowing into the trachea. During sleep, both the swallowing and cough reflexes are diminished and, as a consequence, it is easier for the postnasal discharge to flow into the trachea. Due to this mechanism, postnasal drip is considered to be related to the development of asthma[2,3].

RHINOSINUSITIS AND BRONCHOPULMONARY DISEASES

Rhinosinusitis and chronic bronchitis

A link was found between the presence of chronic rhinosinusitis (CRS) and chronic bronchitis, even if a small number of studies have addressed this connection. Along with the inflammation of the upper and lower respiratory tract mucosa, both CRS and bronchitis share the same risk factors such as smoking or occupational exposure.

Bergqvist et al.[33] performed a five-year longitudinal prospective study to assess the risk of chronic bronchitis in CRS patients. The Telemark study included 7393 subjects who were evaluated via an e-mail questionnaire focused on occupational exposure to different irritating substances, lifestyle, smoking status. The results showed that the presence of CRS was associated with an increased risk of developing chronic bronchitis (CB) during the 5-year survey period (11.8% prevalence of CB in 2018 among patients included in the CRS-positive group from 2013). When considering variables such as age, gender, body mass index, asthma or smoking, CRS-positive patients exhibited an increased odds ratio (OR = 3.8, 95%CI 2.65-5.40) of developing CB compared to the CRS-negative group. The authors also reported an increased risk of CB diagnosis for each additional CRS cardinal symptom developed by the patients.

Rhinosinusitis and COPD

The literature reports a prevalence of sinonasal symptoms in COPD patients between 33% and 88%[34]. However, the link between CRS and COPD, especially with the presence of comorbid bronchiectasis in COPD patients, is still being investigated. The EPOS2020 (European Position Paper on Rhinosinusitis and Nasal Polyps) make no reference to this association[35].

In 2017, Yang et al.[34] assessed the presence of CRS in 136 patients diagnosed with COPD. All patients were evaluated using a questionnaire, sputum samples, paranasal sinus and chest CT scans. Of all patients included in the study, 48.5% were diagnosed with CRS and 47.1% had signs of bronchiectasis on the chest CT scans. 57.6% of the patients with bronchiectasis were in the CRS-positive group and 37.1% in the CRS-negative group ($p = 0.017$). When analysing the patients with COPD and comorbid bronchiectasis, those who associated CRS had a higher severity score for pulmonary pathology compared to those without CRS ($p = 0.034$). All COPD patients, with or without bronchiectasis, showed higher levels of eosinophils, IL-6, IL-8, MMP-9 in their sputum when associated with a CRS diagnosis. Analysis of the questionnaire results showed that the SNOT-20 score positively correlated with the CAT (COPD Assessment Test) score in all patients ($r = 0.315$, $p < 0.01$), while the Lund-McKay score presented a negative correlation with the forced expiratory volume in 1 second ($r = -0.251$, $p < 0.05$) in patients with COPD and CRS.

In 2020, Arndal et al.[36] evaluated the prevalence and the risk of CRS among COPD patients and its impact upon patients' QoL. The cross-sectional study was performed on 222 COPD patients between 2017 and 2019. The results revealed that 22.5% of the patients diagnosed with COPD also had chronic rhinosinusitis, the sinonasal pathology being undiagnosed prior the study in 82% of the cases. The subjective questionnaire showed that the QoL was significantly worse in CRS-positive COPD patients when compared to those without nasal disease ($p < 0.0001$).

It should be mentioned that, in both presented studies, the diagnosis of chronic rhinosinusitis was based on the EPOS2020 criteria[35].

Rhinosinusitis and asthma

The most frequent and important link between rhinosinusitis and asthma has been reported for many years[4]. There seems to be a prevalence of almost 20% of asthma in patients with CRS when compared to the general population (5-8%)[4].

According to EPOS2020, chronic rhinosinusitis is classified into chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP)[35]. Epidemiological, pathophysiological and clinical data support that CRSwNP is more frequently linked with asthma and even coexists with it[4,37,38]. 40-67% of patients with CRSwNP have asthma. In a study performed on 25 adult patients with CRSwNP, 24% were also diagnosed with asthma and 36% with small airways disease[39]. A correlation with the severity of asthma was also found.

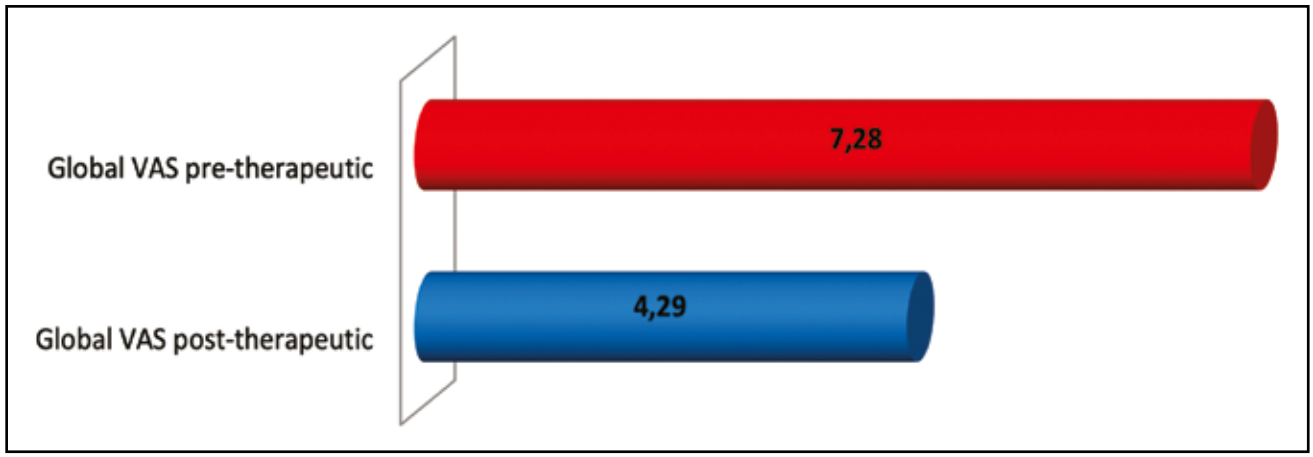

Figure 1. Global VAS evolution in the study population.

Table 1. Evolution of VAS score according to the extracellular HMGB1.

Before and after treatment	Extracellular HMGB1				P-value (Student t-test)
	0	1	2	3	
Nasal obstruction	3.1417±1.1689	2.9700±0.9522	2.7300±1.0242	2.7105±1.2569	0.4267
Nasal pruritus	1.7139±1.0099	1.3100±0.9585	1.8900±0.7852	1.5421±1.1340	0.5388
Rhinorrhea	2.4806±1.0317	2.6700±1.3217	2.5100±1.5220	2.0263±1.3436	0.4121
Sneezing	1.4458±0.8747	1.6300±0.7804	1.8400±1.2349	1.6000±0.7165	0.5448
Ocular manifestations	1.1667±0.7977	1.5800±1.3315	1.3900±1.0929	1.2000±1.0028	0.5491
Global VAS	3.40 [2.70, 4.10]	3.30 [2.80, 3.90]	2.55 [2.20, 3.10]	1.60 [1.00, 1.80]	0.0000
TOTAL	2.00 [1.00, 3.00]	3.00 [2.00, 4.00]	4.00 [1.00, 4.00]	2.00 [2.00, 4.00]	0.1808

Castillo et al.[40] reported a clear association between CRSwNP and severe asthma (35%, p<0.001; OR=3.4, 95%CI 1.68-6.78), while allergic and non-allergic rhinitis, as well as CRSsNP, showed a similar frequency in all asthma severity groups.

The pathophysiological link between nasal polyposis and asthma lies in the type 2 inflammatory reaction, which can be found in both pathologies. Type 2 cytokines (IL-4, IL-5, IL-13) and IgE can be identified in the inflammation at both levels. These immune mediators trigger the accumulation of mast cells, eosinophils, basophils, M2 macrophages and B-cells, which are also responsible for the inflammatory tissue reaction. The eosinophilic inflammation in the nasal polyps and sinus mucosa leads to the formation of pseudocysts with albumin deposition, elevated levels of IL-5 and eotaxin[41]. The IgE concentration level is a severity predictor for both CRSwNP and asthma. In cases of sinus disease, the total serum IgE levels can be correlated, in specific instances, with the mucosal disease visible on the cranio-facial CT scans. The same correlation has been observed for mucus eosinophilia, which also correlates with the degree of nasal polyposis. Elevated levels of eosinophils in the nasal mucosa (>5 cells per high-power filed) are indicative of severe disease and are a predictor of disease evolution for patients who underwent endoscopic sinus surgery[42].

HMGB1 (high mobility group box 1 protein), a proinflammatory protein with alarmin function, proved to be another prognostic factor for the severity of CRSwNP and asthma[43-45]. Secreted by the immune cells such as monocytes, macrophages and dendritic cells, HMGB1 interacts with specific membrane receptors on the surface of macrophages and monocytes (e.g., toll-like receptors TLR2 and TLR4; receptors for advances glycation end-products - RAGE) and activates the intra-cellular signalling mechanism via the transcriptional factor NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells). This triggers the acti-

vation of endothelial cells (high expression of adhesion molecules VCAM-1, ICAM-1), generating an inflammatory reaction.

To investigate if HMGB1 protein is somehow correlated with the severity of the clinical form of rhinosinusal pathology as well as the treatment response, we conducted a two-year prospective study on 111 adult patients (18 - 63 years old) diagnosed with moderate to severe allergic rhinitis and CRSwNP. All patients included in the study performed ENT evaluations (nasal endoscopy, cranio-facial CT scan) and allergological assessments (skin prick tests). A subjective evaluation using a visual analogue scale (VAS) analysed the following parameters: nasal congestion, rhinorrhea, sneezing, ocular symptoms, nasal pruritus and global evaluation, both at the study enrolment and 3 months after treatment. Nasal biopsy samples were taken and immunohistochemistry for identifying HMGB1 protein was performed using a polyclonal anti-HMGB1 antibody. The distribution of the protein in both the nuclear and cytoplasmic cellular compartments, as well as in the extracellular space, was also assessed. The treatment scheme followed by all included patients consisted of intranasal glucocorticosteroids (50µg, 1 spray per nostril, twice daily) for 3 months.

Global VAS decreased by 41.09%, from a mean value of 7.28 before treatment to 4.29 after treatment (Figure 1). Also, the average global VAS score was decreased significantly less in patients with high levels of extracellular HMGB1 compared to those with degree "1" (p-value = 0.0004) or "0" (p-value = 0.0000) (Table 1). When analyzing the severity of the five evaluated parameters in relation to the extracellular presence of HMGB1 protein, we found no statistically significant difference between the groups after treatment: $p = 0.4267$ for nasal obstruction, $p = 0.5388$ for nasal pruritus, $p = 0.4121$ for rhinorrhea, $p = 0.5448$ for sneezing and $p = 0.5491$ for ocular symptoms (Table 1). There was no difference in the changes of the average global VAS score between patients with different degrees of HMGB1 positivity in nuclear and cytoplasmic localization (p-value > 0.1). We concluded that high extracellular levels of HMGB1 protein represent a disease aggressiveness in its natural evolution.

An association of CRSwNP, comorbid asthma and aspirin-exacerbated respiratory disease (AERD) complicates the entire clinical and pathophysiological picture. These patients usually present with severe, more difficult to control asthma, with mucus production, a higher risk of bronchoconstriction, airway hyperresponsiveness, obstruction and increased death risk. They often have recurrent and eosinophil-rich nasal polyposis[37]. According to EPOS2020, all patients with poorly controlled or uncontrolled CRS, allergic and non-allergic rhinitis, and AERD are classified as having severe chronic upper airways disease (SCUAD)[35], which can be associated with severe lower airway syndromes.

HOW TO DIAGNOSE A RHINO-BRONCHIAL SYNDROME?

The diagnosis of a rhino-bronchial syndrome is based, primarily, on the clinical symptoms represented by: chronic cough, dyspnea, posterior rhinorrhea, nasal obstruction, headache, matinal vomiting.

From an ENT perspective, the diagnostic approach includes nasal endoscopy, cranio-facial CT scans, and in a secondary plane rhinomanometry. The pneumologist will insist on collecting clinical data, performing pulmonary function tests and chest imaging. Allergologic examination with skin prick tests and serologic testing can have an essential role in establishing the correct diagnosis.

Passali et al.[2] elaborated an integrated multidisciplinary diagnosis for rhino-bronchial syndrome. A patient presenting to the general practitioner with nasal obstruction and/or nasal discharge, accompanied by cough and/or dyspnea, will receive first-line treatment. If there is no recovery, then the patient should be referred to the ENT specialist or pneumologist.

The recommendation for the ENT specialist is to perform a clinical examination, nasal endoscopy and a CT scan of the nose and sinuses. If the patient presents with dyspnea and cough, and the clinical pulmonary findings suggest recurrent bronchitis, referral to a pulmonologist is advised. If a pulmonary pathology is confirmed, a diagnosis of RBS can be established.

If the patient is seen by a pneumologist, it is recommended to perform a clinical examination, beta-2 agonist test, methacholine test, spirometry and chest imaging (x-ray, CT scan). A patient who, besides cough and dyspnea, also presents with nasal obstruction and posterior rhinorrhea, should raise suspicion of rhinosinusitis and/or pharyngitis and be referred to an ENT specialist. If rhinosinusal pathology is confirmed, a diagnosis of RBS can be established.

IS RHINO-BRONCHIAL SYNDROME DIFFICULT TO TREAT?

The treatment of a rhino-bronchial syndrome implies a correct diagnosis of the primary cause and treatment of the sinonasal pathology. Some

patients are responsive to local or systemic corticosteroids but in most cases, the surgical approach is needed, especially for CRSwNP. In these cases, phenotype and genotype determination is essential in order to develop new treatments and to decrease the use of surgery.

A modern treatment should respect several principles: 1. the etiology, clinical features and stages of the disease, along with patients' comorbidities; 2. CRSsNP and CRSwNP have a different significant clinical evolution; 3. the nature and severity of the inflammation process or damage.

The most important aspect regarding RBS is the fact that a multidisciplinary approach and follow-up are needed (ENT specialist, Pneumologist, Allergologist)[1,2]. The etiological treatment can be medical and/or surgical. The medical treatment addresses bacterial or viral infection, allergy, GERD. Surgery is needed in cases of nasal polyps, anatomical abnormalities or complications.

The medical treatment includes mainly corticosteroids, mucolytics and even antibiotics. Oral antihistamines and aspirin desensitisation can help. In patients with atopy, allergen-specific immunotherapy can be recommended.

Intranasal saline water helps managing the symptoms related to CRS, postnasal drip. Nasal or oral decongestion can be used, but their efficacy did not prove to be higher than saline nasal irrigation.

When GERD is diagnosed, the proton pomp inhibitors are part of the medical treatment plan.

Innovative medical treatments have been developed over the years. The monoclonal antibodies such as dupilumab (anti IL-4Rα), omalizumab (anti IgE) or mepolizumab (anti IL-5) reduce free IgE, down-regulate high-affinity IgE receptors, limiting mast cells degranulation, minimize the release of mediators throughout the allergic inflammatory cascade[46]. This therapy is mainly indicated in severe CRSwNP cases and in patients with symptoms that are poorly or uncontrolled with intranasal corticosteroids.

The surgical treatment is indicated in patients who are non-responsive to steroids, have contraindications to systemic or topical steroid medication, unusual site of origin of the polyps (e.g., nasal septum, turbinates, olfactory cleft), or have complications or associated comorbidities (e.g., severe or poorly controlled asthma or CPOD). The initial severity of the disease is one of the best predictors for the postoperative recurrence of nasal polyps. Another early marker for the need for surgery is the presence of subjective olfactory changes.

It is important to remember that the basic principles of both medical and surgical treatment are to ensure adequate drainage of the paranasal sinuses. Also, it is unrealistic to expect surgery to cure all patients with CRS, which is inherently a "chronic, recurrent, benign disease" that needs periodic follow-up and timely medical management. An extensive immunological evaluation, including IgG subtypes and antibody testing, should be considered in poorly controlled patients.

In paediatric patients with rhino-bronchial syndrome, the risk of cystic fibrosis should not be overlooked.

If diagnosed correctly, the treatment for RBS can have a success rate of up to 94% after 3 months of therapy[2].

CONCLUSIONS

The rhino-bronchial syndrome is a condition characterised by chronic rhinosinusal inflammation and simultaneous chronic pulmonary pathology (asthma, chronic obstructive pulmonary disease, chronic bronchitis). The most prominent association is between sinonasal pathology, particularly allergic rhinitis, and asthma. This is characterized by increased eosinophils infiltration in both the nasal and bronchial mucosa, independently of the allergen- exposure level. Chronic rhinosinusitis, especially when associated with nasal polyps, can be an important risk factor for asthmatic patients, and vice versa.

It is necessary to assess and treat rhinitis and rhinosinusitis in patients with asthma, because these conditions can exacerbate bronchopulmonary symptoms.

Last but not least, patients with rhino-bronchial syndrome need a multidisciplinary approach by a medical team: otorhinolaryngologist, pneumologist and allergologist.

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