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Review

Rhinosinutis and Asthma in Children

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Abstract: Rhinosinusitis and asthma are two comorbid conditions that lead to pathological and clinical diseases affecting the respiratory tract. They are connected by significant anatomical, epidemiological, pathophysiological, and clinical evidence, and also share therapeutic principles. The aim of this review is to provide an updated overview of the existing link between rhinosinusitis and asthma focusing on the pediatric age.

Keywords: rhinosinusitis; asthma; children

1. Introduction

Rhinosinusitis and asthma represent a major public health problem, because of their frequency and their impact on quality of life, school performance and economic burden [1]. According to the latest European Position Paper on Rhinosinusitis and Nasal Polyps, pediatric rhinosinusitis is defined as an inflammation of the nose and the paranasal sinuses characterized by two or more symptoms. These symptoms include nasal blockage, nasal obstruction, nasal congestion, or nasal discharge (anterior or posterior nasal drip), in combination or not with facial pain, facial pressure and coughing; these can be accompanied by either endoscopic signs of nasal polyps (with mucopurulent discharge primarily from the middle meatus and edema), mucosal obstruction primarily in the middle meatus, or computed tomography (CT) changes (as mucosal changes within the ostiomeatal complex or sinuses) [2].

Acute rhinosinusitis (ARS) in children is defined as a sinonasal inflammation lasting <12 weeks and is associated with the sudden onset of symptoms [2]. The vast majority of ARS is due to acute upper airway infections (viruses accounting for up to 90% of the causative agents) and might be aggravated by underlying allergic conditions (i.e., allergic rhinitis) [2].

We usually refer to chronic rhinosinusitis (CRS) when the disease lasts ≥12 weeks without the complete resolution of symptoms [2]. Compared with adults, coughing is a much more significant symptom in children with CRS than a decreased sense of smell. CRS in children may also coexist or be exacerbated by other widespread conditions such as allergic rhinitis, adenoid disease, and gastroesophageal reflux [2]. CRS is often characterized by periods of remission and exacerbation, with a significant impact on patient quality of life (QoL) [3]. CRS is broadly classified into two major phenotypes, based on nasal endoscopic and CT findings: CRS with nasal polyposis (CRSwNP) and CRS *sine* nasal polyposis (CRSsNP) [2].

Recent data have demonstrated that CRS affects approximately 5–15% of the general population in both Europe and the United States [4]. Nasal polyposis (NP) is more frequently seen in men than in women [5], and in adolescents or elderly and asthmatic subjects [6]; it is less common in childhood [7,8]. NP may be either isolated or associated with other medical conditions. Isolated NP in children is a rare condition, representing an alert sign for other underlying systemic diseases (including cystic fibrosis, immunodeficiencies, and primary ciliary dyskinesia) [9].

Pediatric severe chronic upper airway disease (P-SCUAD) is a novel term introduced to define difficult-to-treat cases, characterized by the persistence of upper airway inflammation and symptoms despite correct diagnosis and management [10]. These cases often show a negative impact on quality of life, social functioning, and school or work performance [11]. Although the definition and the pathogenesis of SCUAD in the pediatric population still need to be better clarified, it seems that the presence of important comorbidities, such as adenoid hypertrophy, allergic rhinitis (AR), and asthma, may have an impact on clinical outcomes and contribute to the lack of disease control in CRS patients [10,11]. Adenoids may act as a bacterial reservoir, as well as an active immunological organ in the context of CRS in children [12]. Moreover, emerging evidence has shown that adenoidectomy is effective in controlling symptoms in a proportion of children with CRS [13]. The evidence of an increased incidence of atopic predisposition in pediatric patients with rhinosinusitis, as well as the correlation between allergies and the severity of a sinus disease, have long been supported as a possible causal relationship between CRS and AR [14]. However, few data are available to prove a clear and definitive relationship, especially in children, and it seems that AR is not a trigger for CRS, but rather a comorbidity [14].

Asthma is defined as a heterogeneous condition, with the specific hallmark of chronic airway inflammation. It commonly manifests with symptoms such as coughing, wheezing, shortness of breath and chest tightness, which may change over time and in intensity due to airflow limitation in respiratory airways [15]. Patients can experience episodic flare-ups (exacerbations) that may be life-threatening, usually triggered by factors such as exercise, allergen exposure, weather, or viral infections, and represent a major health problem to patients [15].

The aim of this review is to provide an updated overview on the existing link between rhinosinusitis and asthma focusing on pediatric age.

2. Rhinosinusitis and Asthma in Children

Strong anatomical, epidemiological, pathophysiological, clinical, and therapeutic evidence has recently been revealed regarding the link between upper and lower airways, changing the global pathogenic view of respiratory diseases. The term "united airway disease (UAD)" is used to define this complex interplay [16,17].

2.1. Anatomical Evidence

The respiratory apparatus is anatomically divided into the upper and lower respiratory tracts and has the function of air conduction and gas exchange [6]. Although considered as different entities, the nose and the lung share several microscopic and macroscopic similarities [6]. Histologically, both nose and bronchi are composed of pseudostratified respiratory epithelium with columnar ciliated cells. The basement membrane and ciliary epithelium with glands and goblet cells are present through the whole respiratory tree, all the way to the passage in the respiratory bronchioles with the air cells [16]. This complex anatomical structure makes it necessary to humidify, temper, filter, and supply the air with nitric oxide before entering the gas-exchange region of the lung, protecting the lower respiratory tract from potentially harmful external agents. Rhinosinusitis causes the loss of nasal breathing, a potential trigger for bronchial disorders due to the inhalation of cold and dry air [18]. In addition, the air conduction system plays a central role in protecting the lower tract from inhaled foreign substances, by avoiding the passage of particles of 5–10 μm in diameter [18]. In contrast, mouth breathing leads to increased concentrations of inhaled aeroallergens that may reach the lower respiratory tract, potentially inducing a bronchoconstriction in asthmatic subjects. The communication between the nose and bronchi also seems to be implemented via mechanisms such as neural reflexes and systemic pathways [18].

2.2. Epidemiogical Evidence

There is increasing epidemiological evidence linking asthma to CRS in adults, especially eosinophilic asthma phenotypes and CRSwNP. Adult asthmatic patients, especially those with severe asthma, often have CRSwNP [19]. The presence of NP is associated with the severity of asthma, ranging from 10–30% in mild asthma to 70–90% in severe asthma and regardless of smoking status [20,21]. In the European Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (UBIOPRED) cohort of severe asthma, a high incidence of upper airway symptoms was observed, with the presence of NP in 25% of adult subjects [21]. The impact of upper airway comorbidities on asthma severity and control was also reported in the US Severe Asthma Research Program (SARP) study and in the UK Difficult Asthma National Registry [22]. Epidemiological examinations and evidence-based studies are often lacking in the pediatric population. It was reported that 27% of a series of pediatric patients admitted with status asthmaticus had radiological evidence of rhinosinusitis [23], while in another study, 44% of 128 asthmatic children had evidence of rhinosinusitis upon endoscopic examination [24]. Furthermore, an asymptomatic "occult" sinusal involvement, diagnosed with nasal endoscopy, was demonstrated in 7.5% of an uncontrolled asthmatic children population [25]. Fewer studies have investigated whether asthma affects the upper airways. Dejima et al. showed that children with asthma have worse surgical outcomes after sinus surgery and/or adenoidectomy compared with non-asthmatic children [26]. The impact of upper airway pathology on asthma severity and control was demonstrated in the setting of pediatric non-severe asthma: in pre-school children, untreated or undiagnosed upper airways obstruction, often due to rhinosinusitis and concomitant adenoid hypertrophy, may worsen the obstructive pathology of the lower airways [27]. This data has not yet been confirmed for pediatric studies on severe asthma; the cluster analysis of pediatric SARP reported a higher incidence of comorbidities in cluster 3: the main comorbidities found increased bronchial hyperresponsiveness and lower lung function [28]. This may suggest that phenotypes in children differ from those in adults; they are also known to rapidly change over time.

2.3. Pathophysiological Mechanisms

Asthma and CRS are both heterogeneous disorders with a complex pathophysiology, sharing the common type 2 inflammatory pattern, including Th2 cell induction, interleukin (IL)-5 and IL-13 production, and eosinophilic infiltration [18,29]. A direct relationship between upper (nasal) and lower inflammation was observed in an adult population [30].

Few studies directly investigated concomitant upper and lower inflammation in children. Riccio et al. showed the presence of a typical Th2 cytokine response (increased IL-4 and tumor necrosis factor-α (TNF-α)) in the rhinosinusal lavage in allergic asthmatic children with rhinosinusitis [31]. On the other hand, a reversal of the cytokine pattern from a Th2 to a Th1 profile in both allergic and non-allergic children has been observed after medical treatment of CRS: Tosca et al. looked at the change in levels of IL-4 and interferon-γ (IFN-γ) in rhinosinusal lavage fluid in children with asthma and CRS after a 14-day treatment of oral antibiotics and intranasal steroids and a 10-day treatment of oral steroids. They demonstrated a significant decrease in IL-4 and a significant increase in IFN-γ in allergic study participants, and a significant decrease in IL-4 and a non-significant increase in IFN-γ in non-allergic study participants after the treatment [32]. The inflammatory response in the sinus and adenoid tissues of children with CRS and asthma has been observed as quantitatively amplified by Anfuso et al.: children with CRS and asthma had significantly higher sinus levels of TNF-α as well as adenoid levels of epidermal growth factor, eotaxin, fibroblast growth factor-2, growth-related oncogene, and platelet-derived growth factor-AA compared with children with CRS and without asthma [33].

According to the concept of "united airways disease", airway inflammation may start at one site and extend to other sections eventually, and vice versa. Besides the extension by contiguity, airway inflammation is sustained by a complex interplay among several immunological mechanisms that take place both inside and outside the respiratory system, even involving the bone marrow [34]. In an experimental murine model of eosinophilic asthma triggered by *Aspergillus fumigatus* sensitization, it was demonstrated that,

after intranasal allergen exposure, basophils and Th2 lymphocytes circulate and migrate significantly to several sites, including the bronchial airways, after being released from the storage pools in the bone marrow [35,36]. Thus, triggering inflammation in the airways may stimulate the bone marrow to produce inflammatory cells and mediators that have an effect on respiratory sites other than those affected initially.

Finally, altered breathing patterns, nasal, pharyngeal, and bronchial reflexes, post-nasal drip, and inhalation of polluted or cold air represent other mechanisms that may further exacerbate the inflammatory disease from upper to lower airways, although they did not end up being the main determinant of comorbidity between CRS and asthma [37].

A better definition of inflammatory pathways of both childhood CRS and asthma is needed in order to recognize the linked pathophysiologic mechanisms of both diseases.

2.4. Clinical and Therapeutic Management

The impact of the presence and severity of upper airway pathology on both asthma severity and control has been demonstrated in several studies [38,39]. In particular, reduced asthma control increased airway obstruction and impaired QoL are the main items in asthmatic patients with CRS [3,38–40]. On the other hand, previous pediatric studies focused on asthma outcomes when rhinosinusitis is treated pharmacologically [41]. An improvement of asthmatic symptoms, lung function and airway hyperresponsiveness has been more recently confirmed after rhinosinusitis therapy in children with both diseases [31,42]; in particular, an improvement in both asthma QoL and control has been experienced in patients presenting with CRS refractory to medical therapy and coexistent asthma after endoscopic sinus surgery (ESS) procedures [43].

CRS and NP have also been both identified as independent risk factors for frequent asthma exacerbations in adults [44,45]. In the large SARP cohort study, CRSwNP were significantly associated with exacerbation frequency [46]. Subsequently, CRS symptom severity has been associated with asthma-related oral corticosteroid use [47].

Early identification of an upper airway disease is crucial for asthmatic patients at risk of more severe disease. Thus, an ear, nose, and throat (ENT) specialist evaluation with a nasal endoscopy and imaging is mandatory to confirm or rule out the clinical suspicion of sino-nasal involvement. As in adults, untreated sinus disease may also contribute to unstable asthma control in childhood. Thus, children with difficult-to-treat or severe asthma should be actively screened for comorbid disorders, in particular those involving the upper airways. Finally, all patients with uncontrolled asthma should be assessed for the possibility of upper airway disease, even in the case of minimal or absent symptoms [48].

Diagnostic biomarkers have been proposed as indicators of type 2 inflammation, such as serum total immunoglobulin E (IgE), eosinophilic cationic protein (ECP), eosinophils, and cytokines IL-4, IL-5 and IL-13, all detectable in blood and from now on in nasal secretions [34]. Higher levels of mucosal and blood eosinophils (together with comorbid asthma), IgE, ECP, and IL-5 have been correlated with the recurrence of the nasal disease, acting as prognostic biomarkers in CRSwNP [49,50]. Furthermore, the presence of *Staphylococcus aureus* and its enterotoxin-specific IgE has also been proposed as a risk factor for co-morbid asthma and for recurrence of NP after surgery [51].

As for asthma, achieving and maintaining the clinical control of the disease is the primary goal of a CRS treatment. Control is defined as a disease state in which patients exhibit negligible symptoms with the minimal effective local therapy, in the presence of a healthy or almost healthy nasal mucosa, as stated in the latest European Guidelines on Sinusitis and Nasal Polyposis (EPOS) [2]. Corticosteroids, and especially topical corticosteroids, in conjunction with nasal saline irrigation represent the mainstay of treatment for patients with CRSwNP or CRSsNP, even at the pediatric age, while the use of systemic corticosteroid therapy is burdened by a significant risk of side effects, such as insomnia, weight gain, gastrointestinal symptoms, adrenal suppression, osteoporosis, steroid-induced diabetes mellitus, and growth retardation in children, especially for prolonged therapy [2]. Other therapies, such as antibiotics, antihistamines, and leukotriene receptor antagonists, have not yet proven to be effective in

reducing signs and symptoms of CRSwNP [2]. In case of failure of medical therapy, functional ESS might be indicated with satisfactory but temporary results [2]. Recurrence of disease after surgery has been reported to be as high as 80%, in particular in patients with CRSwNP and increased eosinophil counts, IL-5 and IgE in nasal tissue [52]. Therefore, surgery must always be accompanied by medical therapy, since topical corticosteroids may slow down the recurrence of mucosal inflammation.

Despite all possible therapeutic measures, a subgroup of patients, characterized by severe and recurrent CRSwNP and comorbid asthma and identified by a type 2 immune response (IgE, eosinophils, IL-5 and IL-4/IL-13), may remain uncontrolled and require further innovative therapy. For those patients, biological agents may represent a future valuable alternative, as they can simultaneously control symptoms of both upper and lower airways [53]. While anti-IgE and anti-IL-5 monoclonal antibodies now have an established position in the therapeutic management of severe asthma, an indication for biologics in chronic uncontrolled upper airway diseases has not yet been provided. However, monoclonal antibodies against IgE, IL-5, and IL-4 or IL-13 pathways (omalizumab, mepolizumab, and dupilumab) have been tested with promising results in recent proof-of-concept studies performed in adult patients with CRSwNP with or without asthma; the first adult studies on phase III of these biotherapeutics are still running and may disclose new and significant treatment options to target both upper and lower airway disease [43].

As for precision medicine in asthma, a step forward towards the tailored management and therapy of patients with chronic upper airway inflammation has been recently proposed, with the aim of improving care and preventing asthma [54]; a dedicated approach to the pediatric age is still lacking and may represent a future area of research.

3. Conclusions

Rhinosinusitis and asthma are closely related to each other in many aspects, sharing not only common pathophysiological mechanisms but also therapeutic principles. As in adults, a cluster of chronic upper airway comorbidities is also recognized in childhood asthma, including chronic rhinosinusitis. Undiagnosed and untreated chronic rhinosinusitis may contribute to worsen asthma control and complicate diagnostic and therapeutic management of asthmatic patients. Early recognition of upper airway disease in asthmatic patients is also crucial to identify patients at risk of more severe disease. The possibility of upper airway disease should be ruled out in all patients with uncontrolled or troublesome asthma, even in the case of minimal or absent symptoms.

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