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Short review

Pediatric rhinosinusitis and asthma

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ABSTRACT

Both asthma and rhinosinusitis are complex and heterogeneous diseases and, importantly, they often coexist: these diseases can be concomitant in 35–65% of affected children, according to different studies. Thus, evaluating this comorbidity in the clinical practice should be paramount. In this review, we focused our discussion on the multiple pathophysiological aspects that may link rhinosinusitis and asthma in the pediatric population. Although rhinosinusitis may exacerbate asthma through several mechanisms occurring by contiguity, actually this aspect seems to be only one component of the complex interplay between upper and lower airways. In particular, the onset of an important and persistent Th2-driven inflammatory process dominated by eosinophils presence at one site of the airways, may release into the bloodstream several cytokines; in their turn, those can lead to the stimulation of the bone marrow, which may function as a systemic amplifier of such an eosinophilic inflammation.

1. Introduction

Sinusitis generally refers to the inflammation in the nasal sinuses and, as it is usually associated with the inflammation of nasal mucosa (namely, rhinitis), the term rhinosinusitis (RS) is currently considered to be more appropriate [1].

It is important to underline that RS is not exclusively a disease of adulthood: indeed, RS must be suspected in both pediatric and adult patients complaining of nasal symptoms, such as nasal congestion and/or rhinorrhea, persisting for more than 7–10 days without any improvement. Such a temporal cut-off is useful to distinguish RS from self-limiting upper respiratory infections (URIs), caused by viral agents: these latter clinical conditions can show the same pattern of symptoms, but usually resolve by 7–10 days [3–5]. By definition, the symptoms of acute RS (ARS) resolves within 3–4 weeks; if sinus inflammation persists (regardless of the medical management), it could evolve to chronic RS (CRS), defined by a disease duration longer than 8–12 weeks [1,2].

Therefore, the diagnosis of RS often relies on clinical findings only, including the duration of nasal symptoms, the characteristics of nasal discharge (e.g. purulent) and the presence of other manifestations, such as facial pain and fever. Computerized tomography (CT) is required whenever the suspicion of extra-sinus complications should arise [6–9]. Moreover, in patients with CRS, CT can also permit the detection of nasal polyps in the sinus cavities, as nasal endoscopy can identify those protruding in the nasal cavities. According to the endoscopic and/or radiological findings, there are CRS forms without nasal polyposis (CRSsNP) and others with nasal polyposis (CRSwNP). Epidemiological evidences suggested that CRS is especially prevalent among patients with asthma, in addition to patients with immunodeficiency, cystic fibrosis and aspirin allergy [9–11].

In this review, we will discuss the complex relationship linking RS and asthma in children. We aim at providing a comprehensive overview on the current evidences deriving from pediatric studies and, then, at analyzing those in light of the interplay among the multiple immune-pathological aspects that may be implicated.

2. Epidemiological aspects

Although the respiratory system has been traditionally divided into upper and lower tracts, actually many patients complaining of respiratory diseases often show an extensive involvement of both sections. For instance, rhinitis and asthma frequently coexist. As regards RS, a number of studies have evidenced its association with asthma since 1920s; importantly, several studies suggested the importance of RS in triggering and/or worsening asthma in both adults and children [12,13].

Recently, the study by Matsuno et al. reported the prevalence of RS diagnosis in the general asthmatic population, as being 36.7%. Interestingly, sinus CT abnormalities were detected in 66.3% of patients with asthma: although these CT findings were reported much more

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frequently in patients with moderate to severe asthma, actually also some patients with intermittent or mild persistent asthma were found to have concomitant sinus inflammation. In general, patients with severe and persistent asthma were 14.3% among those diagnosed with RS, whereas such a percentage decreased to 3.8% in patients without RS [14]. Previously, other studies evidenced the frequent occurrence of CRS in adult patients with severe and steroid-dependent asthma. In particular, Crater et al. estimated the prevalence of RS in asthmatic patients as comprised between 35% and 45%; additionally, mucosal thickening in sphenoid, ethmoid, and frontal sinuses was significantly more common in asthmatic patients than in controls, represented by people evaluated for non-respiratory diseases [15–18]. Unfortunately, here it was not possible comparing the prevalence of sinus abnormalities between asthmatic patients and those with isolated URIs.

Similar findings have been reported in the pediatric population. However, the number of pediatric studies is much fewer than for asthmatic adults. Recently, our group described 294 consecutive asthmatic children (mean age, 7.3 years) investigated by nasal endoscopy: occult sinus involvement was demonstrated in 7.5% of cases, who resulted to have poorly controlled asthma [19]. Actually, the comorbidity between RS and asthma in children has been noticed for several decades. In 1994, Fuller et al. demonstrated that 27% of children admitted to the hospital with severe asthma had abnormal findings on sinus radiograph [20]. One more recent study by Tosca et al. showed that about 50% of children diagnosed with persistent asthma presented concomitant RS by nasal endoscopy [21].

Therefore, the association between RS and asthma seems to be quite clear: especially children and adolescents affected by poorly controlled asthma should be investigated for occult or manifest RS by nasal endoscopy and, eventually, by CT, if appropriate. However, it is still debated whether such an association is due to a causal relationship, meaning that RS is part of the etiology of asthma, or actually asthma and RS are different pathological and clinical manifestations of the same underlying disease process, according to the so-called United Airways Disease concept [22].

3. Rhinosinusitis as a causative factor of asthma

The main argument supporting the role of RS - and CRS in particular -, as a co-causal or worsening factor of asthma is the improvement of its control after the resolution of sinus disease, through the appropriate medical therapy or surgery (e.g. functional endoscopic sinus surgery, FESS), if needed [2,23].

Back to 1984, Rachelefsky et al. showed that 79% of children (aged 4–13 years) with poorly controlled asthma were able to discontinue bronchodilators after the medical treatment of CRS: moreover, 67% of children normalized their pulmonary function tests, too [24]. Similar findings were reported in a set of smaller studies, where most children receiving medical treatment for concomitant RS improved their asthma control [21,25–27]. Oliveira et al. reported that children affected with RS improved their bronchial hyper-responsiveness to methacholine, and decreased their asthma symptoms after the medical treatment of RS [28]. The prospective study by Tsao et al. including 41 children medically treated for CRS, showed an increase of the provocative concentration of methacholine causing 20% fall in FEV1, compared to pre-treatment values. Again, children undergoing surgical management for CRS showed an improvement of their lower airway disease [29]. In the study by Parsons et al. including 52 pediatric patients, there was a 96% decrease in asthma symptoms assessed by a retrospective interview, in addition to the significant reduction of monthly asthma exacerbations and of emergency room visits, after the surgical management of CRS [30]. In the study by Manning et al. including 14 steroid-dependent children with asthma and CRS, most of them showed improvement in their asthma control after FESS [31].

Thus, a number of clinical evidences suggested that CRS influences the course and/or the occurrence of asthma. Several mechanisms may explain this relationship: i) nose-pharynx-bronchial reflexes; ii) post-nasal drip with drainage of inflammatory mediators into the lower airways; iii) inhalation of polluted and/or cold and/or dry air into the lower airways [32].

Nose-pharynx-bronchial reflexes in human and animal models can occur after nasal stimulation with a variety of substances and physical agents. The stimulation of receptors in the nose, pharynx and also in sinuses may generate nervous signals transmitted to the central nervous system, through afferent fibers of the trigeminal nerve; such a signal may be elaborated in the brainstem in order to generate a reflex efferent signal via the parasympathetic nervous system, affecting bronchial muscle tone and, ultimately, inducing lower airways constriction [12,33]. Rolla et al. showed that the damage of the pharyngeal mucosa in patients with CRS (mediated by the drainage of inflammatory mediators and cells and/or of infected material, probably) increased the exposure of sub-mucosal nerve to irritants, leading to the activation of the reflex arc [34].

As for the post-nasal drip, it could not be limited to the pharynx and its effects might extend to lower airways directly; however, those few available studies have not clearly supported this hypothesis. Indeed, Bardin et al. showed that there was no pulmonary aspiration of sinus content in patients with concomitant asthma and RS, through a study carried out by the placement of radionuclide into the sinuses [35]. Actually, through a similar study approach, Ozcan et al. reported some degree of pulmonary aspiration of radionuclide-labelled nasal secretions during sleep, but the difference between patients with comorbid asthma and sinusitis, and the healthy patients recruited as a control group, was not significant [36].

Finally, the possibility that the loss of function of inflamed/infected sinuses may result in the impairment of air modifications is quite intriguing, in light of some recent evidences. Abnormal breathing (excluding the passage of air throughout the sinus system) impairs air warming, humidification and purification from pollutants and irritants: that may allow physical factors and chemical agents to act on the lower airways [37]. Moreover, in allergic patients, the impairment of air filtering in presence of sinus disease might also increase the allergen load reaching the bronchial system. Actually, research studies testing primarily this hypothesis are not available, yet. However, Papp et al. compared the nasal-air conditioning between patients with CRSwNP (before and after sinus surgery) and healthy control subjects: the nasal heat increase and humidification was significantly lower before surgery in patients compared to controls. Interestingly, patients showed a significant improvement in the heating capacity of the nasal airways 4–6 weeks after surgery, but there was no significant improvements in nasal humidification [38].

4. Inflammation in asthma and CRS

Infectious-related and/or immune-mediated inflammatory mechanisms may be variably implicated in the etiology and pathogenesis of CRS.

Whereas in ARS infections – probably the superimposition of bacterial infections on a preceding viral illness – represent the main causative factor, in CRS a primitive non-infectious inflammatory mechanism may provide the pathological basis, where super-imposed infections may contribute to the perpetuation of the chronic inflammation. Impaired epithelial functioning, altered innate and adaptive immunological interplay with environmental agents (including microorganisms and pollutants), and tissue re-modelling may be all contributive factors to the development of CRS. A recent large population study showed a familial risk in children with CRS. Another study suggested a role for two airway epithelial potassium channels as susceptibility loci for CRS; anyway, it is known that children with immunologic disorders, ciliary dyskinesia and cystic fibrosis are predisposed to suffer CRS [39–41]. Importantly, antibody deficiency is an important immunologic factor contributing to a continuous