Current Allergy and Asthma Reports (2019) 19: 13
https://doi.org/10.1007/s11882-019-0843-9

RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Multimorbidities of Pediatric Allergic Rhinitis

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Published online: 22 February 2019
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Abstract

Purpose of Review Most children and adolescents with allergic rhinitis (AR) present extra-nasal multimorbid conditions, including conjunctivitis, asthma, atopic dermatitis, rhinosinusitis, or seromucous otitis. Additionally, they may present nasal obstructive disorders, such as septal deformity, turbinate enlargement, and adenoidal hyperplasia, which worsen nasal symptoms, especially nasal obstruction. This is a narrative review on the current state of the concomitant presence of AR and one or more multimorbidities.

Recent Findings The presence of AR and one or more accompanying multimorbidities is associated to a higher severity and duration of the disease, a negative impact on quality of life, with worse control and lack of improvement with medical treatment. Therefore, AR needs to be managed with a multidisciplinary collaborative approach.

Summary Pediatric AR needs to be considered in the context of a systemic disease, which requires a coordinated therapeutic strategy.

Keywords Pediatric allergic rhinitis · Septal deformity · Turbinate enlargement · Adenoids · Asthma · Atopic dermatitis

Introduction

Allergic rhinitis (AR) is the most frequent chronic condition in childhood and adolescence in the developed world. Its prevalence is increasing, affecting up to 40% of global population [1]. In pediatric population, AR prevalence reaches 8% in 6–8-year-old children and increases up to 35% at 13–14 years old [2, 3].

More than 75% of AR children develop concomitant conditions, including conjunctivitis, asthma, atopic dermatitis, rhinosinusitis, otitis media with effusion (OME), or adenoid hyperplasia (AH), indicating AR is not an isolated condition, but it is part of a systemic disease (Tables 1 and 2).

Multimorbidity is defined as the presence of one or more chronic conditions coexisting with a primary disease [16]. When the primary organ is not known, such as in allergic diseases, the term multimorbidity should be used instead of comorbidity [17].

Although there have been significant improvements in delivery of care for allergies, many quality improvement activities, clinical guidelines, and innovations have focused on the needs of patients with single allergic conditions. However, multimorbidity is increasingly prevalent, and represents a major part of the workload of AR management (Table 1).

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This article is part of the Topical Collection on *Rhinosinusitis*

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Table 1 Diagnosis of multimorbidities associated with pediatric allergic rhinitis

Multimorbidity	Clinical suspicion	Diagnostic tests
Septal deformity	Persistent nasal obstruction is the main symptom, predominantly unilateral. Absence of response to medical treatment. History of nasal trauma	Anterior rhinoscopy. Nasofibroscopy or nasal endoscopy when possible
Turbinate enlargement	Nasal obstruction of variable intensity and alternating laterality. Absence of response to medical treatment. Hyposmia	Anterior rhinoscopy and nasal endoscopy when possible. Nasal obstruction VAS, nasal peak flow, and anterior rhinometry pre and post vasoconstrictor may help define a mucosal or bony anatomical disorder
Adenoidal hyperplasia	Nasal obstruction, mouth breathing, snoring, adenoid fascies, associated otitis media serosa	Posterior rhinoscopy, nasofibroscopy or lateral cavum radiograph when this is not possible
Rhinosinusitis	Nasal obstruction/congestion, purulent rhinorrhea, hyposmia, headache/facial pressure, cough	Nasofibroscopy. Sinus CT scan is not recommended unless there is a suspicion of complications, unilateral symptoms, or lack of response to medical treatment
Asthma	Cough, wheezing, dyspnea, exercise-induced bronchospasm	Peak inspiratory flow, spirometry (preferably with reversibility testing with the use of an inhaled bronchodilator). If there is doubt, provocation tests such as exercise or methacholine, or exhaled nitric oxide measurements
Atopic dermatitis	Cutaneous itching, eczema, redness, rashes. Chronic or recurrent	Clinical diagnosis: facial, cervical, and limb extensor eczema in young children. Eczema in axillary and/or inguinal folds at any age
Food allergy	Rhinitis symptoms related to food intake. Allergic reactions triggered by mouth of pharynx contact with nuts or, which can be tolerated when cooked	Skin prick or patch test. Serum specific IgE. Controlled oral exposure/provocation testing
Conjunctivitis	Ocular hyperemia or pruritus, epiphora. Observe if the patient rubs his/her eyes	Skin prick or patch test. Serum-specific IgE. Slit lamp ophthalmological examination (dilated conjunctival blood vessels, *subtarsal papillae*, keratitis). Conjunctival smear, lacrimal IgE. Conjunctival provocation test
Otitis media with effusion	Language delay, increase TV volume, shouting, poor concentration, poor school performance, recurrent acute otitis media	Otoscopy (pneumatic if possible), acumetry, tympanometry, and audiometry (with visual reinforcement in young children)

VAS visual analogue scale, *CT* computed tomography, *IgE* immunoglobulin E, *TV* television

A recent study analyzed differences between allergic children and adults, concluding that AR in children is more intermittent and severe, with less symptoms but with a higher number of multimorbidities when compared with adults [18]. Additionally, it has been demonstrated that nasal obstructive disorders (NOD) may influence severity, control, quality of life (QoL), and medical treatment response of AR in children and adolescents [6•, 14].

The aim of the present narrative review was to summarize the current state of the concomitant presence of AR and one or more multimorbidities, as well as their impact on severity, QoL, and control of the disease in pediatric population.

AR Multimorbidities

Nasal Obstructive Disorders

Nasal obstruction is a very important symptom in nasal diseases, produced by a reduced airflow in nasal cavities caused by an anatomic and/or inflammatory condition [19]. Nasal obstruction is the core symptom of AR. It is the symptom with higher impact in patient's QoL and the main reason for medical consultation [20]. Additionally, it is the main symptom associated with medical refractoriness in pediatric AR [6•]. NOD, such as septal deformity (SD), turbinate enlargement (TE), and adenoid hyperplasia (AH), may be present in childhood and cause nasal obstruction.

Septal Deformity

It is one of the most common causes of nasal obstruction, and one of the most frequent anatomical disorders in humans. Up to 90% of adults [21] and 30% of children [22] have some degree of SD. There is a wide variety of SD which can distress the quality of nasal breathing in different ways, potentially requiring a specific surgical management in order to accomplish predictable and successful outcomes [23].

The anterior part of the septum, together with caudal margin of the upper lateral cartilage, the floor of the pyriform aperture, and the head of the inferior turbinate constitute the nasal valve area, which is the narrowest portion of the nasal

Table 2 Main recent studies about extranasal multimorbidities in pediatric allergic rhinitis

Author	Study type	Patients	Results
Asthma			
Ibáñez et al. 2013 [4]	Multicentre, observational, transversal	1275 children 6–12 years old with AR in 271 centers	Nearly 50% of the children had asthma. Patients with persistent, moderate, or severe AR were more likely to present comorbidities
Pinart et al. 2014 [5]	Prospective cohort, multicentre	16,147 children 4 yeas old and 11.080 children 8 years old	The relative risk (RR) of developing any comorbidity at age 8 years ranged from 36.2 for children with rhinitis and eczema at age 4 years to 63.5 for children with asthma, rhinitis, and eczema at age 4 years
Mariño-Sánchez et al. 2017 [6•]	Prospective, real-life	130 children and adolescents (6–18 years old) with PER	Good control of asthma significantly increases the probability of AR improvement with medical treatment (OR = 2.3; CI95%: 0.2–1.2; $p = 0.008$)
Kou et al. 2018 [7]	Meta-analysis including 25 transversal studies	Chinese pediatric population	Incidence of asthma in children with AR: 35% (CI95%: 32.3–37.7%). Incidence of AR in children with asthma: 54.9% (CI95%: 53.1–56.8%)
Atopic dermatitis			
Viñas-Domingo et al. 2004 [8]	Prospective, transversal	57 boys and 43 girls. Mean age of onset of AD was 1.09 ± 1.69 years	35% of children developed respiratory allergic disease (asthma and/or AR) in mean time of 2.55 years after AD onset. Moreover, 55.3% of children sensitized to inhalant allergens (Dpt) developed respiratory symptoms, compared to 22.6% of children not sensitized ($p < 0.001$); OR: 4.2 ($p = 0.002$)
Ćosićkić et al. 2017 [9]	Prospective, observational	114 AD children followed for 5 years to study comorbidities	31.6% developed asthma, with a mean age of 7.7 years; 24.9% presented AR symptoms; 11.4% suffered both AR and asthma
Gray et al. 2017 [10]	Prospective, observational	100 South African AD children aged 6 months to 10 years	39% presented asthma symptoms and 53% AR symptoms. Children were sensitized to indoor allergens (house dust mites, epithelia) from an early age. Allergies to pollen, asthma and AR increased with age, according to the allergic march pattern
Otitis media with effusion			
Pau et al. 2016 [11]	Prospective, transversal	159 children with AR and 185 children without AR were evaluated for OME	7.5% of the AR group presented OME compared with 1.6% of the non-AR group ($p = 0.016$). At 3 months of follow-up visit, 85.7% of AR patients showed resolution of their OME
Allergic conjunctivitis			
Gradman et al. 2006 [12]	Retrospective	458 children aged 5–15 years (mean 9.4 years) with AR, asthma, or eczema	30% had allergic conjunctivitis, from whom 97% had AR, 56% asthma and 33% eczema. 91% of children with allergic conjunctivitis had positive evidence of allergy to one or more allergens (house dust mite was the most frequent in chronic allergic conjunctivitis)
Devillier et al. 2016 [13]	Observational, multicentre	253 children (6–11 years old), 250 adolescents (12–17 years old) and 303 adults (18–65 years old)	Ocular pruritus was the most troublesome symptom in children (35%), adolescents (22%), and adults (16%) and was associated with worse QoL outcomes in all groups. Nasal obstruction and nasal itching were associated with a worse QoL only in children and adolescents
Valls-Mateus et al. 2017 [14]	Prospective, real-life	142 children and adolescents (6–18 years old) with PER	The presence of conjunctivitis was associated with worse QoL scores in all domains, except the emotional domain in adolescents and the activities domain in the children
Food allergy			
Friedlander et al. 2013 [15]	Prospective observational	300 children with asthma from inner-city schools followed by clinical evaluation	24% presented physician-diagnosed food allergy, and 12% multiple food allergies. Children with food allergies had increased asthma morbidity and decreased lung function, with a stronger association in those with multiple food allergies

AR allergic rhinitis, *yr* years, *PER* persistent allergic rhinitis, *AD* atopic dermatitis, *OR* odds ratio, *CI* confidence interval, *QoL* quality of life, *OME* otitis media with effusion, *Dpt Dermatophagoides pteronyssinus*

passage. Therefore, deformities of the valve area, such as an anterior or a bilateral SD, in a swollen allergic nose with hyperplasic and inflamed turbinate mucosa, may severely impair the dynamics of nasal airflow [24].

Nasal septum morphology in AR patients responding to medical treatment is mostly similar to that in the general population. However, in children and adolescents AR refractory to medical treatment present a higher prevalence of unilateral anterior or bilateral obstructive SD. These types of SD are strongly associated with a higher AR severity and a lower response to medical treatment [25].

In children with severe obstructive SD, a conservative endonasal septoplasty has demonstrated to improve QoL [26] and to be a safe procedure with no impairment on maxillofacial growth [27]. We have found no studies in the current literature about the effect of septoplasty on AR children. We must be aware that, in addition to medical treatment, septal surgery might be insufficient in these patients and it may be often complemented with turbinate surgery.

Turbinate Enlargement

Inferior turbinates are the initial point of allergen deposition where inflammatory cascade starts, triggering changes that will cause nasal congestion or obstruction [17]. In allergic patients, turbinates may considerably enlarge because of an increase in the number of cells (hyperplasia), vessel dilation, fibrosis, and inflammation [28].

The NODPAR study (*Nasal Obstructive Disorders in Pediatric Allergic Rhinitis*) [6•] evaluated medical treatment response based on the presence or absence of NOD in children and adolescents with persistent AR (PER). We observed the group of patients not responding to treatment recommended by guidelines (intranasal corticosteroids (INCS), antihistamines, and antileukotrienes) had a higher prevalence of obstructive SD and TE, associated to a higher AR severity. Severe TE was strongly associated with higher intensity of nasal congestion, rhinorrhea, and smell loss. In addition, an inverse association was observed between medical treatment response and nasal obstruction evidenced by nasal endoscopy [6•].

In children with PER, obstructive TE is an independent factor that increases more than five times the risk of unresponsiveness to INCS treatment [6•]. The presence of allergenic receptors in the turbinate mucosa triggers the release of nasal and systemic inflammatory mediators, which leads to subepithelial inflammation and irreversible fibrosis of inferior turbinates. Additionally, turbinal inflammation mechanically hinders the distribution of INCS into the nasal cavity [29]. This may explain why patients with NOD do not respond adequately to intranasal medical treatment.

Due to its primary implication in the pathophysiology of nasal obstruction, the inferior turbinate has been the target in the surgical treatment of AR. A variety of turbinoplasty techniques have been used to decrease the volume of inferior turbinates with good therapeutic results in AR patients [30].

Turbinoplasty improves nasal obstruction but also other symptoms such as rhinorrhea, sneezing, nasal itch, hyposmia, and overall nasal function [31]. It has also shown to be a safe procedure in children [32]. However, it is necessary to maintain medical treatment with INCS after surgery, since long-term recurrence is frequent because surgery does not treat the cause of the disease.

Adenoidal Hyperplasia

Upper airway persistent allergic inflammation may cause lymphoid hyperplasia, leading to an increase in the volume of the adenoid tissue. The presence of local allergic inflammation, including the synthesis of total and specific IgE [33], a prominent eosinophilic inflammatory pattern, and the presence of lymphoid cell populations [34] have been described in the adenoid tissue of children with AR.

Evcimik et al. [35] compared 1322 allergic children (mean age 5.9 ± 3.3 years) with 100 non-allergic children. AH was assessed by nasofiberendoscopy or lateral nasopharyngeal radiography. The frequency of AH in allergic children was higher than 12%, whereas in non-allergic children it was only 3% ($p = 0.003$). In addition, the presence of allergic tests positive to aeroallergens was strongly associated with the presence of AH.

Contrariwise, in another study, Ameli et al. [36] observed in 205 children (4–12 years old) an inverse relationship between the presence of allergy and AH, whereas the presence of TE was associated with the absence of AH.

A recent study evaluated the influence of AH on the severity and duration of AR in 566 atopic children. They observed a higher frequency of PER in children with AH. In addition, most children with AH had moderate-severe AR [37]. In the NODPAR study [6•], all cases of obstructive AH belonged to the group of patients not responding to medical treatment; however, the differences were not significant, probably due to the low number of pre-school and school children where AH is more prevalent. These clinical observations suggest that PER is an inflammatory recurrent disease that can cause AH, which may increase resistance to medical treatment.

Acute and Chronic Rhinosinusitis

According to EPOS *(European Position Paper on Rhinosinusitis and Nasal Polyps)* criteria [38], chronic rhinosinusitis (CRS) in children is defined as inflammation of the mucosa of the nose and paranasal sinuses, characterized by the presence of at least two symptoms, one of which should be nasal congestion or nasal discharge, with facial pain and/or loss of smell and/or cough during at least 12 weeks, and

endoscopic signs or changes in computed tomography (CT) compatible with sinus involvement. Acute rhinosinusitis (ARS) is distinguished from CRS by the duration of symptoms for less than 12 weeks. Many of these symptoms, such as nasal congestion, rhinorrhea, loss of smell, and cough, are usually present in PER, which makes it difficult to accurately discriminate the diagnosis when nasal endoscopy or CT scan is not available.

The relationship between rhinosinusitis and respiratory allergy is controversial. AR has been described as a comorbidity in pediatric CRS [39]. Several studies have reported that atopy markers are more prevalent in children with CRS [40–42]. However, due to the heterogeneity used in the different studies for the definition of both CRS and AR, the role of AR in CSR is still debated [43].

Nguyen et al. analyzed the prevalence of CRS in allergic children with chronic (> 3 months) sinonasal symptoms, and concluded that AR was not a risk factor associated with CRS [44]. These findings were confirmed by another study in which the diagnosis of CRS was done by CT scan [45]. In 2006, Leo et al. studied 351 children diagnosed with CRS according to the EPOS criteria. They found a prevalence of sensitization to at least one aeroallergen in the prick test and increased blood IgE values in only 30% of children, similar to the prevalence in the pediatric general population [46].

There are only two recent studies on the role of AR in ARS. Lin et al. studied prospectively 69 children aged 3–12 years for a period of 1.5 years. Of these, 27 children (40%) with AR were more likely to suffer episodes of ARS than non-atopic children [47]. In a recent study, Leo et al. prospectively evaluated the incidence of ARS during the pollination season of grass in 242 children with intermittent AR. Seventeen allergic children (7%) were diagnosed with ARS confirmed by nasofibroscopy, while 3 of 65 non-allergic children (4.6%) had ARS in the control group ($p = 0.4$). They concluded that intermittent exposure to grass pollen in atopic children during the pollination season does not increase the risk of ARS [48•]. The role of the PER in ARS, however, has not been clarified.

Smell Loss

Loss of smell is a very common symptom in AR patients. AR has been associated with moderate hyposmia in both adults [49] and children [50] with a prevalence near 50%. Olfactory loss seems associated with a higher duration and severity of rhinitis, probably due to a mixed etiology in which two mechanisms are involved: nasal obstruction (increased difficulty for odor particles to reach the olfactory neuroepithelium) [51] and mucosal inflammation (increased concentration of local inflammatory mediators) [49]. After medical treatment, olfactory improvement seems to be more linked to anti-inflammatory than to nasal patency changes [52].

In a recent study [53], 150 children and adolescents with PER were evaluated using a VAS for smell loss. More than 60% ($n = 87$) of patients reported subjective loss of smell. The intensity of hyposmia was significantly higher in patients not responding to medical treatment and in patients with severe PER. In contrast, patients with controlled AR had a lower prevalence and intensity of loss of smell. In addition, smell loss was associated with the presence of NOD such as severe TE or the combination of TE and obstructive SD. These findings suggest that the loss of smell in pediatric AR patients is associated with an increased disease severity and worse response to medical treatment, probably linked to the presence of inflammatory and anatomic NOD [53].

Asthma

AR and asthma are considered as two different clinical expressions of the same inflammatory IgE-mediated disease, affecting the entire respiratory tract [1]; hence, the concept of "united airway" is currently universally accepted [54]. Consequently, it is advisable to assess the concomitant existence of asthma in patients with moderate–severe PER. The development of asthma during childhood (early onset) is usually associated with allergy, but in adulthood (late onset) they are usually independent [18]. Both AR and non-allergic rhinitis (NAR) have been associated with asthma development. Once both entities are diagnosed in the same patient, we should take into consideration that poorly controlled AR might aggravate asthma and increase health care consumption because of bronchial symptom exacerbations [7, 55]. A study conducted in adult asthmatics demonstrated nearly 90% had AR. Furthermore, a correlation between severity of both conditions was found, the prevalence of AR being inversely correlated to patient's age and asthma severity [56]. Likewise, poor asthma control is associated with an increased risk of medical treatment failure in children and adolescents with PER [6•].

Tran et al. [57] recently reported that the presence of atopic dermatitis and allergic sensitization in combination, but not atopic dermatitis alone, is associated with an increased risk of asthma at age 3 years. Therefore, the development of childhood asthma is highly associated with allergy. Moreover, adult-onset asthma is often non-atopic [58]. The conclusion of a 14-year longitudinal study to identify risk factors of adult-onset asthma was that neither pre-existing atopy nor new atopy was associated with adult-onset asthma [59].

Most patients with asthma suffer from a concomitant upper airway condition [1], such as AR, NAR, or CRS [38]. There are not many structural differences between the ciliated epithelium of the upper and lower respiratory tract. AR and asthma are both characterized by the presence of a similar inflammatory process in which mast cells and eosinophils are the main effector cells [38]. Other possible etiologic mechanisms

to explain the link between AR and asthma are the loss of nasal function (inspired, purified, heated, and humidified air), the nasobronchial reflex (nasal irritants, allergens, or cold stimuli) [17], the theory of rhinovirus adhesion (increased susceptibility to allergic inflammation and expression of the intracellular adhesion molecule (ICAM)-1 [60], and "migration "of T cell response to other tissues after initial sensitization [17]. The postnasal drip theory (transportation of inflammatory mediators from the nasopharynx to the lower respiratory tract) has been abandoned, since this drip ends up in the digestive tract, after its passage through the larynx, and not in the lower respiratory tract [17].

Furthermore, it has been recently described that small airway respiratory dysfunction precedes the development of asthma in children with AR [61•]. Changes in respiratory impedance during AR exacerbation could help identify those patients at risk of progressing to asthma.

The Allergic March

The allergic march describes the natural history of atopic disease in a sequence of IgE-dependent clinical manifestations, with different symptoms but an identical pathogenesis that follows a defined path related to the patient's age. In infants, it initially starts as a food allergy and/or atopic dermatitis and afterwards as respiratory sibilants, in pre-school and school children as AR which may be accompanied of conjunctivitis, and in older children as bronchial asthma and later on with other atopic diseases [62].

A European study with more than 20,000 children showed that the coexistence of eczema, asthma, and rhinitis in the same child is more frequent than expected. Children with one of these diseases at the age of 4 years were four to seven times more likely to have two or three of them at the age of 8 years. Furthermore, children with two or three allergic diseases at the age of 4 years were 30–60 times more likely to have two or three of these diseases at the age of 8 years [5].

The allergic march is strongly linked to a family history of asthma, allergic rhinoconjunctivitis, atopic dermatitis, or food allergy. Recently, genetic risk factors such as mutations in filaggrin have been related to this allergic syndrome in some patients [63]. The role of an immunologically active and dysfunctional cutaneous barrier is probably fundamental in the evolution of allergic responses in atopic patients with relevant environmental exposures. Further understanding of the connections defining the allergic march will lead to earlier diagnosis and appropriate treatment of children at risk to develop effective strategies for the prevention of allergy [62].

Atopic Dermatitis

Atopic dermatitis (AD) is an inflammatory disease characterized by itchy skin lesions. The pathogenesis of AD includes alteration of epidermal barrier function, immune deregulation, food-mediated IgE sensitization, and environmental allergens. In the International Study of Childhood Asthma and Allergy (ISAAC) [3], the prevalence of AD in children varied significantly between 0.3% and 20%, but an increasing trend in the incidence of the disease was demonstrated in recent decades. AD usually occurs in the first few years of life; 45% of children develop the condition during the first 6 months of life, 60% during the first year of life, and up to 85% before the age of 5 years [3].

In a Croatian study in 114 children with AD for 5 years to evaluate the onset of allergic respiratory diseases, children with AD were found to have an increased risk of developing asthma and AR. Additionally, authors reported that increased absolute eosinophil count and IgE specific to aeroallergens and food allergens were the best predictors of asthma, while the predictors of AR were family history and early onset of AD [9]. There is evidence to support the hypothesis that deterioration of the skin barrier and early AD may play a causal role in the development of sensitization and diseases such as asthma and AR [64]. Several studies are currently ongoing with the hypothesis that regular and prophylactic use of emollients may significantly decrease AD expression. These studies are also exploring whether the decreased expression of AD could modulate the allergic response and, consequently, modify the association between early onset AD and the subsequent development of allergic airway disease and food allergies. In Gray et al.'s study, 100 children with AD were followed to determine the prevalence and sensitization patterns to aeroallergens, asthma, and AR. The authors found that pollen allergies increased with age, while allergies to house dust mites and pet epithelium were more frequent in younger children, related to early exposure through a defective skin barrier. If confirmed, the use of neonatal emollients could be a simple public health measure to reduce the incidence of AD, AR, asthma, and food allergies in future generations [65••]. Hence, it seems clear that AD is an early and important step in the evolution of allergic march which triggers food and respiratory allergy through epicutaneous allergen sensitization [10].

Allergic Conjunctivitis

The ocular surface is the most environmentally exposed mucosal membrane of the body. Conjunctives are easily accessible to allergens, and consequently suffer numerous allergic reactions [66]. It is estimated that 33–56% of allergic conjunctivitis coexists with AR [1, 12]. Allergic response may be generated in the conjunctiva itself or in the nose through mutual anatomical connections between the nasal mucosa and the ocular surface [67]. It is more frequent in patients sensitized to seasonal allergens [66].

Cooccurrence of conjunctivitis with PER in children and adolescents worsens QoL outcomes [14]. In a recent study, Devillier et al. evaluated 806 patients (253 children, 250 adolescents, and 303 adults), 83.5% with moderate–severe AR to grass pollen. Eye itching was the most bothersome symptom in children (35%), adolescents (22%), and adults (16%). Eye symptoms had a negative impact on the QoL of all three age groups [13]. Eye symptoms associated with AR are often under-diagnosed and inadequately treated.

Allergic conjunctivitis should be considered a different entity that imposes its own burden on patient's medical costs and QoL, especially in those with moderate to severe persistent PER symptoms [68].

Food Allergy

Food allergy is defined as a variety of adverse immune responses triggered by certain food proteins. There are numerous types, each with particular clinical manifestations and pathogenesis. Food allergy affects 1–10% of general population, although it is not clear whether prevalence is increasing [69].

Several risk factors have been reported, including gender (male sex in children), ethnicity/ancester (higher among Asian and Afroamerican children compared to Caucasian children), genetics (family associations, HLA, and specific genes), atopy (comorbid AD), vitamin D deficiency, dietary fat, reduced intake of antioxidants, use of antacids, obesity (inflammatory condition), improved hygiene, and the timing of food exposure [70].

Food allergy usually precedes respiratory allergy, and it can be a risk factor for AR and asthma as well as a clinical marker for severe extrinsic asthma [15]. Moreover, the presence of coexisting asthma can enhance life-threatening symptoms that occur during a food allergic reaction [71]. Furthermore, respiratory sensitization may cause food allergy, as demonstrated by pollen-related allergies or wheat allergy induced by the use of wheat protein soap [70]. Skin exposure to environmental food allergens can also be a route of sensitization, particularly when there is an epithelial barrier dysfunction, such as in patients with AD [72].

Otitis Media with Effusion

Recent clinical evidence suggests that atopy and AR are risk factors for OME [11], and that medical treatment of allergy may improve otological symptoms [73]. Furthermore, age seems to be an effect modifier between AR and OME, existing significant association in children aged ≥ 6 years, but not in younger children [74].

Proposed mechanisms for association between AR and OME include inflammation generated by allergy in the respiratory epithelium at the entrance and within the Eustachian tube, with subsequent tubal dysfunction [75]. In addition, the middle ear mucosa also appears to be involved in the allergic response, as suggested by the united airway concept [76].

Quality of Life

AR, despite not being a life-threatening disease, has a major impact on QoL, disrupting social life, self-esteem, and school performance [77], leading to absenteeism, loss of work productivity, impairment of concentration, and learning capacity [78]. Therefore, QoL deterioration is used as a parameter to define the severity of the disease.

Nasal obstruction is the most common and bothersome symptom of AR, since it strongly affects QoL. The pathophysiology and symptoms of pediatric AR often disrupt sleep, leading to fatigue, irritability, memory impairment, daytime sleepiness, and depression [1, 79].

Children with AR tend to be shy, depressed, anxious, or fearful [79]. Adolescents with AR have QoL issues similar to those of adults, but they have fewer sleep problems and more concentration issues (particularly with schoolwork). In addition, they are often concerned about practical problems such as carrying handkerchiefs or taking medication, but they do not report as much interference with day-to-day activities or emotional disturbances as adults [80].

The impact of AR on QoL has been explored through generic and specific questionnaires. One of the best known is the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), which has been validated in several countries in its various versions, including the PRQLQ (pediatric) [77] and the AdolRQLQ (adolescent) [80]. These specific AR questionnaires allow physicians to identify major problems to evaluate other issues not verbalized by the patient.

Devillier et al. [13] studied the QoL and symptom profile of 806 AR patients (253 children, 250 adolescents, and 303 adults). They used the Rhinoconjunctivitis Total Symptom Score (RTSS), the VAS, and the RQLQ questionnaire. Nasal obstruction and nasal itching were associated with poor QoL in adolescents and children, demonstrating a different perception of symptoms between these age groups and adults [13].

In recent study [14] in pediatric patients with PER (6–11-year-old children and 12–17-year-old adolescents), our group analyzed different variables (QoL, NOD, comorbidities) comparing patients responding to medical treatment with non-responders. Both non-responder adolescents and children reported worse QoL scores than responders. In adolescents, the most affected domains were nasal symptoms and activities. In children, nasal symptoms were also the most affected domain of PRQLQ, followed by practical problems. Additionally, a strong correlation ($R > 0.5$, $p < 0.05$) was found between symptoms measured by VAS and the overall QoL score in both children and adolescents [14]. These

findings are in line with those of previous studies [81, 82], where they have described a clinically relevant deterioration of QoL in non-responder patients, corroborating the usefulness of RQLQ instruments [77, 80] for evaluating QoL in treated pediatric patients.

Regarding gender, significant differences have been found in QoL scores among adolescents. Worse female gender scores in this age group [14] support a previous consideration that women are more likely to report symptoms and to have poorer self-assessment of health [83]. Kalpaklĩoğlu et al. [84] studied the impact of AR and asthma on QoL. Female gender was a risk factor for impaired QoL in both diseases. Occasi et al. [85] described gender differences in the subjective perception of nasal discharge in patients aged 6–14 years, so that women estimated their nasal patency more accurately when comparing symptoms scores and rhinomanometric results.

In our study [14], girls (< 12 years old) also had worse PRQLQ scores than boys but the differences did not reach statistical significance, pointing at adolescence as the period of life in which these gender differences might appear. Another factor associated with worse QoL in adolescents, but not in children, was the presence of obstructive septal deviation and obstructive turbinate hyperplasia. Additionally, the presence of conjunctivitis affected negatively both children and adolescents [14].

Conclusions

Pediatric AR is frequently associated with multiple extra-nasal disorders such as conjunctivitis, atopic dermatitis, asthma, rhinosinusitis, OME, or food allergies, which indicates that AR is not an isolated condition but it is part of a systemic inflammatory process. Additionally, children and adolescents with AR often present NOD such as SD, TE, or AH, which can worsen nasal symptoms, increase disease duration and severity, and decrease response to medical treatment, therefore worsening QoL. Consequently, pediatric AR should be considered a disease with a high multimorbidity that needs to be managed with a coordinated multidisciplinary team (pediatricians, immuno-allergists, dermatologists, pulmonologists, and otolaryngologists) to reach a more accurate diagnosis and, thereby, better management decisions that translate to improved clinical outcomes.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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