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Chapter 2

Epidemiological Aspects of Rhinitis and Asthma: Comorbidity or United Airway Disease

Sanela Domuz Vujnovic and Adrijana Domuz

Additional information is available at the end of the chapter

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Abstract

Bearing in mind the results of the epidemiological studies, the logical question arises whether allergic rhinitis represents an earlier clinical manifestation of allergic airway disease or itself is causative for asthma. Comorbidity or one disease, the diagnosis of allergic rhinitis often precedes the development of asthma. Literature reports that 40–90% of asthmatics have symptoms of allergic rhinitis. The epidemiological evidence also suggests that allergic rhinitis and asthma radially presented one united airway disease with two-stage than two separate diseases. Symptoms of one disease often predominate and are unrecognized or hidden of another disease even if they exist. The epidemiology evidence of comorbidity of allergic rhinitis and asthma confirmed the new concept of the united airway diseases. Despite the evidence of the correlation between allergic rhinitis and asthma, there is some resistance in clinical practice in recognizing this link.

Keywords: asthma, allergic rhinitis, united airway disease, epidemiology, prevalence, comorbidity, respiratory symptoms

1. Introduction

We have to agree with Togias [1] that the respiratory system has been one of the victims of fragmented medical knowledge. The respiratory system is most often viewed as two separate systems, upper and lower. These have resulted in lost opportunities to fully understand the function of the respiratory system [1]. Upper and lower respiratory systems have similarities in histology, physiology, and pathophysiology [2]. The nose warms, filters, and humidifies inhaled air. Impaired air warming and humidification by the nose may cause bronchoconstriction. A reduced function of the nose can be caused by congestion forces the patient to

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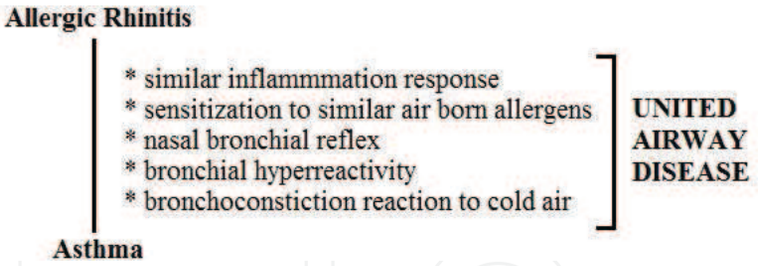


Figure 1. Possible link between asthma and allergic rhinitis.

mouth breathing. Also, there are similarities in inflammation response between allergic rhinitis and asthma [3, 4]. Allergic rhinitis and asthma are frequently associated with sensitization to similar airborne allergens [5]. Some authors suggest the existence of a nasal-bronchial reflex as a cause of bronchial reactivity in a patient with nasal inflammation [6, 7]. That's why recent studies suggest new theory or concept that these two diseases should be viewed as united diseases (**Figure 1**) [8, 9]. The epidemiology evidence of comorbidity of allergic rhinitis and asthma confirmed the new concept of the united airway diseases.

Comorbidity of allergic rhinitis in asthmatics results in frequent emergency visits, asthma exacerbation, asthma-related hospitalizations, and higher asthma-related medical costs [4]. Despite the evidence of the correlation between allergic rhinitis and asthma, there is some resistance in clinical practice in recognizing this link [10]. Also, the guidelines for the treatment of allergic rhinitis and asthma are inconsistently implemented. The consequences of this are a very large number of patients with inadequate diagnosis, no treatment, and poor control of the disease [11, 12].

Most of the epidemiological studies investigate only one allergic disease, asthma or rhinitis. In these studies, another allergic disease was not observed as a comorbidity or a confounding factor. Studies that consider asthma and rhinitis as comorbidity are scarce, but the results of available studies showed that these two diseases are in a high percentage in comorbidity. The percentage of comorbidity showed continuity through different ages of the respondents. A high percentage (70–90%) of rhinitis symptoms in asthmatics was presented in children and the elderly population [13–15].

Despite its high comorbidity, there are surprisingly scarce studies about the treatment of AR in children with asthma or vice versa [14, 15]. Children with allergic rhinitis comorbidity were more likely to have incomplete asthma control in Groot et al. study [15].

2. Epidemiological evidence for the link between allergic rhinitis and asthma

The World Health Organization (WHO) through the Allergic Rhinitis and its Impact on Asthma (ARIA) program tried to understand the possible links between allergic rhinitis and asthma [16]. According to the ARIA study, patients with severe persistent rhinitis more likely

have comorbidity with asthma [16]. Epidemiological evidence also suggests coexistence of asthma and allergic rhinitis in the same patients [17]. Symptoms of one disease often predominate and are unrecognized or hidden of another disease even they exist [2]. The epidemiological evidence also suggests that it is radially one disease with two stages than two separate diseases. Underdiagnosis of allergic rhinitis in asthmatics patients is common. Comorbid allergic rhinitis has a clinically relevant effect on asthma, especially on hospitalization and emergency visits [12]. Treating allergic rhinitis in these patients decreased asthma-related medication utilization [17]. Patients with allergic rhinitis also can be underdiagnosed with asthma [12].

2.1. Prevalence of allergic rhinitis and asthma

The prevalence of allergic rhinitis and asthma has increased worldwide over recent decades [13, 18].

Studies appear to indicate that the changes in the prevalence of allergic rhinitis and asthma differ, but they were not designed to show the variation of the link between these two diseases [16]. Epidemiological studies have no standard set of diagnostic criteria for allergic rhinitis or asthma, so it is very difficult to compare the results. Most of the studies used a questionnaire to define a prevalence, or they are self-reported-based study.

2.1.1. Asthma

A number of epidemiologic studies have reported striking differences in asthma prevalence. The largest multicentric study on asthma prevalence in children the International Study of Asthma and Allergies in Children (ISAAC) showed the asthma prevalence increment trend in children in the period from 1994 to 1999 [19]. The lowest asthma prevalence symptoms values in children aged 6–7 years were in the Indian subcontinent, while the highest asthma prevalence symptoms were in Latin America, North America, and Oceania [19, 20]. For the older age group (13–14 years), the lowest prevalence was in the region of Asia and Pacific, Eastern Mediterranean, and the Indian subcontinent, while children from North America had the highest frequency of asthma symptoms [19, 20]. Wheezing prevalence in the last 12 months also had a similar movement trend, with the lowest prevalence in North and Eastern Europe (5%) and the highest in the region of Latin America and Oceania (>20%) [19]. However, a different trend pattern of severe asthma symptom prevalence movement was noticed. Africa, the Indian subcontinent and Eastern Mediterranean had the highest asthma prevalence characterized with a severe form of asthma in children, while children in Latin America had the lowest prevalence of severe asthma symptoms [19]. Twenty-one centers that participated in the multicentric study had the asthma prevalence in children larger than 20%, while seventeen centers had the prevalence lower than 5% [19, 21].

Generally, the prevalence of asthma in children showed the northwest-southeast gradient movement [22]. This kind of trend is especially expressed in eastern continent. The results of ISAAC study show the highest asthma prevalence in English-speaking countries and Latin America and the higher prevalence in West compared to East Europe and the lowest in Asia

and Africa regions [19]. The Great Britain has the highest asthma prevalence in children (32%), then Bulgaria, Czech Republic, Ireland, and Norway. The prevalence in Albania and Greek was the lowest (<5%) [19, 21].

Prevalence of asthma among the elderly population was 10.9% in the study by Pite et al. [13]. The prevalence of asthma increased with the number of rhinitis symptoms, from 2.1% in no rhinitis symptoms group to 44.4% in nasal symptoms plus ocular symptoms group [13].

2.1.2. Allergic rhinitis

Allergic rhinitis has increased in prevalence during last decades with the highest prevalence among children and adolescents [7, 23–25].

The prevalence of rhinitis among the 6- to 7-year-old children was 6.4% in Eastern and Northern Europe and 7.3% in Western Europe [26]. Higher prevalence of rhinitis symptom was among older children (13–14 years old) where 10.5% children in Eastern and Northern Europe and 14.5% in Western Europe have rhinitis symptoms. Children from Georgia had the lowest prevalence (2.8%), while children from Polish (18.9%) and Isle of Man (20.2%) had the highest prevalence of rhinitis [26]. It was found that countries with a low prevalence of asthma also had a low prevalence of rhinitis [26]. In addition to the European continent, the highest prevalence of rhinitis was observed in younger children in Latin America (12%) and older children on the African continent (21.7%). The lowest prevalence of rhinitis in the 6- to 7-year-old children was in Africa (3.6%) and the Indian Subcontinent (3.9%) while in older children in the Indian Subcontinent (10%) [26].

The recent studies suggest a higher prevalence of rhinitis among the middle-aged population (20–28%) [23, 25, 27]. Pite et al. study showed that rhinitis was a highly prevalent but underdiagnosed and undertreated disease in the elderly population [13]. About 80% of patients had rhinitis symptoms, but only half of them had a diagnosis and/or treatment [13].

2.2. Comorbidity of allergic rhinitis and asthma

Epidemiological studies show significant comorbidity of these two diseases. Literature reports that 40–90% of asthmatics have symptoms of allergic rhinitis, while patients with allergic rhinitis have significantly less prevalence of asthma symptoms (10–40%) (**Figure 2**) [16, 28].

However, it should be emphasized that the prevalence of allergic rhinitis in asthmatics is significantly higher than in the general population (10–20%). Conversely, there is a significantly higher prevalence of asthma symptoms among patients with allergic rhinitis than the general population (an average of 5–15%). The association between allergic rhinitis and asthma had been examined in several studies. The strength of the association with asthma increased with increased persistence and severity of rhinitis [13]. The prevalence of asthma increased with the number of rhinitis symptoms, from 2.1% in no rhinitis symptoms group to 44.4% in nasal symptoms plus ocular symptoms group [13]. A French study showed that 58% of asthmatics children had symptoms of allergic rhinitis [30]; the Italian study showed even higher percentage (70%) [29]. Prevalence of allergic rhinitis in patients with classic asthma was 50–69% in the

study by Tajiri et al. [4]. Among patients with physician-diagnosed asthma, 64% had allergic rhinitis in the study by Eriksson et al. [31]. Symptoms of allergic rhinitis were more common if asthma symptoms were more severe [30, 32]. Children with exercise-induced asthma have a significantly higher prevalence of allergic rhinitis symptoms [32]. The epidemiological evidence consistently demonstrates the coexistence of allergic rhinitis and asthma [17].

The majority of asthmatic patients have seasonal or persistent allergic rhinitis [17, 33]. Also, the presence of allergic rhinitis in asthmatics has been confirmed as a marker of asthma severity [32, 33]. A higher prevalence of allergic rhinitis was observed among children who reported at least four wheezing episodes in the last year or sleep disorders due to acute episodes [32, 34]. Consequently, better asthma control can be achieved if the diagnosis and treatment of allergic rhinitis are adequately done [15]. Comorbidity of allergic rhinitis and other variant forms of asthma (cough variant, exercise-induced) has also been observed in epidemiological studies [4, 32]. Many patients with allergic rhinitis do not have symptoms of classical asthma, but they present with airway hyperresponsiveness and subclinical inflammation of the lower respiratory airway [35]. The results of previous studies showed that almost 50% of patients with bronchial hyperreactivity reported no respiratory symptoms [36]. These patients usually develop asthma but remain underdiagnosed with asthma [12, 28]. Also, allergic rhinitis is not appropriate recognition in patients with asthma [28, 37]. Many patients with allergic rhinitis self-manage the symptoms or do not recognize allergic rhinitis as a condition needing treatment or physicians help [12]. The Portuguese study showed that more than half of patients with rhinitis symptoms had no diagnosis by a physician [13]. This shows that these patients are untreated for allergic rhinitis. It is important to emphasize that patients with mild forms of allergic rhinitis or asthma remain in high percentage without diagnosis and adequate treatment [32]. Esteban et al. found in their study that 53% asthmatics children were underdiagnosed with allergic rhinitis, and asthma was not well controlled in 77% of these children. Only 33% of the children with allergic rhinitis diagnosis were receiving a treatment by ARIA recommendations. Children with poorly controlled allergic rhinitis had poorer asthma control [11].

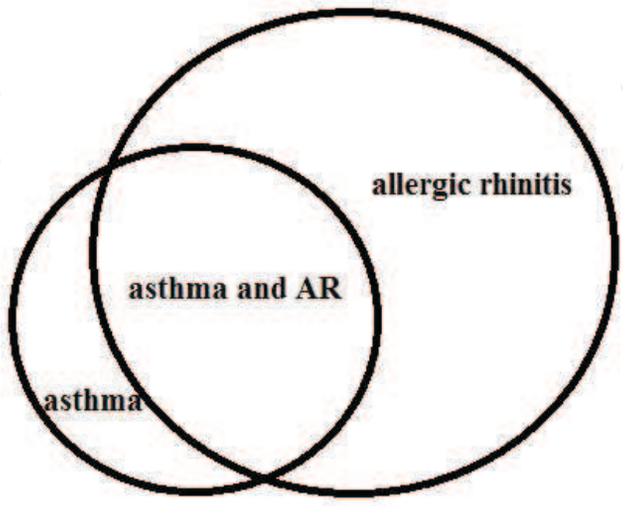


Figure 2. Prevalence and comorbidity of allergic rhinitis and asthma.

Untreated allergic rhinitis in asthmatics contributed to severity symptoms, exacerbation, and uncontrolled asthma [16, 28]. The authors reported that treatment of allergic rhinitis was associated with reduced risk of emergency visits and hospitalization for asthma [3].

3. Allergic rhinitis as risk factor for asthma

Bearing in mind the results of the epidemiological studies, the logical question arises whether allergic rhinitis represents an earlier clinical manifestation of allergic airway disease or itself is causative for asthma [16, 17]. Comorbidity or one disease, the diagnosis of allergic rhinitis often precedes the development of asthma [4, 12]. Studies undoubtedly suggest that allergic rhinitis is a risk factor for asthma [4]. A pathophysiological mechanism which can explain the increased risk of developing asthma in patients with allergic rhinitis is airway hyperresponsiveness. Even 40% of patients with allergic rhinitis showed hyperreactivity to methacholine challenge. Such patients are at greater risk to develop asthma during the next 4–5 years [12]. Also, allergic rhinitis during childhood was associated with increased risk of asthma development in preadolescence and adolescence [28]. The Children's Respiratory Study showed that allergic rhinitis in the first year of life was associated with a risk of developing asthma by 6 years of age [38]. The study by Settipane et al. showed that significantly more (10.5%) of the students diagnosed with allergic rhinitis went on the develop asthma compared with those who did not have allergic rhinitis (3.6%) [39]. The presence of bronchial hyperresponsiveness increased the risk for severe symptoms of allergic rhinitis and asthma and earlier development of asthma in children with allergic rhinitis [12]. It is important to recognize bronchial hyperresponsiveness as a marker of prognostic significance [17]. Epidemiological studies suggest that patients with bronchial hyperresponsiveness without symptoms of classic asthma are more often underdiagnosed with asthma [28].

4. Atopic march

The concept of the atopic march was developed to describe the progression of atopic disorders from atopic dermatitis (AD) in infants to allergic rhinitis and asthma in children [40, 41]. The theory of atopic march implies that young children with atopic dermatitis or food allergy may develop airway allergy such as asthma or allergic rhinitis later in life [40, 42].

The concept of atopic march has been supported by cross-sectional and longitudinal studies [40, 42]. Atopic dermatitis as the first step in the development of atopic march occurs in 45% of children in the first 6 months of life and during the first year of life in 60% of children. In children with atopic dermatitis in the first 2 years of life, an average of 50% of these children develops asthma during subsequent years [42]. The occurrence of only one allergic manifestation, such as recurrent wheeze, eczema, or food allergy, during infancy, was associated with a good prognosis, where over 70% were symptom-free at 8 years of age. Among the children with two or more of any allergic manifestations in infancy, more than half had any allergic disease at 8 years of age [43]. In addition, comorbidity increased from infancy to 8 years of age

as a consequence of the increasing prevalence of asthma and allergic rhinitis. Furthermore, the more allergic manifestations a child had in infancy, the greater the risk of allergic disease and comorbidity at 8 years of age [43]. In late adulthood, allergic symptoms generally become less frequent and tend to disappear, but in some, new-onset allergy or asthma may develop in old age [44]. Results of studies showed that the mean age at onset of atopic comorbidities was 1.8 ± 1.0 years for food allergy, 2.2 ± 1.1 years for asthma, 2.3 ± 1.3 years for allergic conjunctivitis, and 2.4 ± 1.3 years for allergic rhinitis [45]. A systematic review of the literature by van der Hulst et al. showed that there is an increased risk of developing asthma by 6 years among children with eczema [46]. The pooled OR for the risk of asthma after eczema, compared with children without eczema, in birth cohort studies was 2.14. In eczema cohort studies, the prevalence of asthma by the age of 6 years was 29.5%. The proportion of children with eczema developing asthma is clearly higher than among those without eczema, and the "rates" for asthma are three- to fourfold higher than in the general population [46]. However, asthma develops in only approximately one in every three children with eczema. Kapoor et al. examined the prevalence of allergic rhinitis and asthma in 2270 children with physician-confirmed AD and found that by 3 years of age, nearly 66% of the subjects reported to have allergic rhinitis, asthma, or both, and the presence of these diseases correlated with poor AD control [47]. These results should be interpreted with caution because of the heterogeneity of the cohorts.

The Tasmanian Longitudinal Health Study investigated the influence of eczema on the development of asthma from childhood to adult life and found that childhood eczema was significantly associated with new-onset asthma in three separate life stages: preadolescence (hazard ratio 1.70; 95% confidence interval 1.05–2.75), adolescence (2.14; 1.33–3.46), and adult life (1.63; 1.28–2.09) [48]. Results from another two cohorts studies, the Melbourne Atopic Cohort Study (MACS) and the LISAplus study, showed that food sensitization in the first 2 years of life increased the risk of subsequent asthma and allergic rhinitis (MACS OR = 8.3 for asthma and aOR = 3.9 for allergic rhinitis; LISAplus OR = 14.4 for asthma and OR = 7.6 for allergic rhinitis) [49].

The risk of developing atopic diseases is complex, and the temporal pattern described in the atopic march may not be a simple progression [40, 43]. Studies found that many individual children do not follow the classical allergic march [49, 50]. For this reason, different patterns of allergic morbidity and the coexistence of the different manifestations, rather than progressive development of one underlying disease, have been suggested [43]. Several studies have suggested that, even though they are associated, the different combinations of allergic manifestations seen over time suggest the coexistence rather than the progressive development of the same underlying disease [43]. Children with early eczema who develop asthma and allergic rhinitis might represent one specific phenotype of eczema, characterized by eczema plus either wheezing or a specific pattern of sensitization [43]. The results of MAS Study showed that children with eczema and without early wheeze were not at increased risk for the development of asthma. These results implied that eczema alone may not be the first most predictive phenotype in the atopic march [51]. Eczema before 2 years of age without the cofactor of wheeze before the age of 3 years and without a specific pattern of atopic sensitization was not associated with an increased risk of wheezing at 7 years of age (adjusted OR 1.11). In addition, the authors suggest that the combination of eczema with early wheeze is a distinct phenotype

rather than a representation of a progressive pattern of atopic diseases [51]. However, the risk for development of asthma at 7 years of age among children with early eczema and atopic sensitization to less common antigens but without concomitant wheeze was stronger (adjusted OR, 6.68) than the association between early eczema with early wheezing (adjusted OR, 2.84). This is in consistent with the pattern of the atopic march in which eczema with atopic sensitization presents a higher risk for the development of atopic respiratory disease [52]. The cohort of children with an early-onset AD with a lower rate of sensitization to allergens was associated with a low risk for developing asthma. The cohort of children with multiple sensitizations and with familiar history of asthma had a higher prevalence of asthma than the general population in the study of Amat et al. [53]. Also, studies showed that patients with eczema with specific IgE antibodies to common environmental allergens present by 2 to 4 years of age are at higher risk for progressing in the atopic march to allergic rhinitis and asthma than those with eczema without IgE sensitization [53, 54]. Current evidence suggests that further refining early childhood eczema phenotypes may represent a more robust measure of the first phenotype of the atopic march, with a greater predictive value of identifying those at risk of developing allergic rhinitis and asthma [52].

Likewise, many studies in animal models demonstrate that epidermal barrier dysfunction can be caused by repeated sensitization to allergens to the skin, which leads to phenotypes of AD systemic sensitization and increased risk of allergic rhinitis lung inflammation and airway hyperresponsiveness [43]. A study in a mouse model showed that epicutaneous aeroallergen exposure induces systemic Th2 immunity that predisposes to allergic nasal responses, suggesting that the skin is a potent site for antigen sensitization in the development of experimental allergic rhinitis [43]. Experimental studies showed that epicutaneous sensitization with ovalbumin induced AD and airway hyperresponsiveness to methacholine after challenge with aerosolized ovalbumin [43].

The pathophysiological mechanism of atopic march has been unknown. Skin barrier dysfunctions can explain partly the mechanism of atopic march [50]. Namely, skin barrier defect can promote entry for allergens [50]. Epicutaneous sensitization to aeroallergens has been thought to be responsible, with subsequent migration of sensitized T cell into the nose and airways, for development of allergic upper and lower airway diseases [55]. Sensitization that followed eczema is likely to be a step in the pathophysiological pathway between eczema and asthma [56]. Previous data support the hypothesis that respiratory allergies are secondary to allergic sensitization that occurs after epidermal skin barrier defect [50].

4.1. Conclusion

The atopic march is a useful paradigm to describe the clinically observed progression of atopic diseases in certain children [52]. Whether each step in the march is necessary for progression to the next or further defining of these phenotypes would be more useful in identifying children at risk for developing chronic allergic diseases is still a matter of debate. Allergic manifestations can develop at any point in life. Many children will experience only one or perhaps two atopic manifestations, and the development of these can be interspaced by several years [57]. The progression of allergic disease is not uniform in all atopic children. However, the

coexistence of allergic manifestations in the same child has been shown to be more common than expected by chance alone [43]. Also, it is still unclear why some infants with AD outgrow the disease with increasing age, whereas others will march to develop other allergic diseases [41]. Therefore, it is not uncommon that an adult with "new-onset" asthma are unable to remember whether they had allergic diseases in childhood [57]. A better understanding of what places a subset of children with eczema or allergic rhinitis into the risk group for developing asthma is critically important. "Given that most infants with eczema or early wheezing do not develop rhinitis and asthma, further refinement of these early phenotypes or additional risk factors is important for them to be useful" [52]. It is important to define more precise phenotypes of the early stages of the atopic march that may improve its utility in predicting the development of later atopic diseases [52].

Although it has become evident that the mechanisms by which allergen exposure occurs through impaired skin barriers can initiate systemic allergy and predispose individuals to AD, allergic rhinitis, and asthma, the mechanisms of the atopic march are still largely unknown [41]. The findings of studies support the atopic march theory on a population level. But the concept of atopic march is not the strongest factor at the individual level of children with allergic disease [43].

Author details

Sanela Domuz Vujnovic[1]* and Adrijana Domuz[2]

*Address all correspondence to: drdomuz@gmail.com

1 School of Applied Medical Sciences, Prijedor, Republic of Srpska, Bosnia and Herzegovina

2 Primary Health Center, Republic of Srpska, Bosnia and Herzegovina

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