

ORIGINAL ARTICLE

The natural course of allergic rhinitis: a 32-year follow-up study

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Abstract

Conclusion: Early intervention may change the natural course of allergic rhinitis, preventing the progression to asthma. In particular, immunotherapy guarantees remission of local symptoms and valid protection against local and bronchial complications. Symptomatic treatment represents a valid alternative; it is always to be preferred to abstention from any treatment. **Objectives:** Data emerging from various studies on the increase of the prevalence of allergic rhinitis in recent decades appear to be widely dishomogeneous. Another point that needs clarification is the relationship between allergic rhinitis and lower airways pathologies such as asthma or bronchitis. **Methods:** We followed the evolution of allergic rhinitis in a group of patients for the last 30 years to highlight the efficacy of different treatments in the prevention of complications, specifically asthma. After 32 years (1980–2012), 46/73 (63%) patients completed the follow-up. **Results:** Symptomatic drugs exhibited maximum efficacy from the third to the eighth year, with 13 of 15 patients reporting an improvement of symptoms; immunotherapy achieved the best efficacy starting from the sixth to the tenth year (8 of 10 patients recovered). Subsequently, improvements decreased in the two groups, to a steady level of 11 of 15 and 6 of 10 recovered patients. Asthma developed in 3 of 46 patients and only among patients that were not treated.

Keywords: Allergens exposure, asthma, bronchitis, rhino-otitis, eosinophil, symptomatic drugs, skin test, immunotherapy, antihistaminics, corticosteroids

Introduction

The relationship between upper and lower airways pathologies is still controversial. Epidemiologic data indicate that asthma and allergic rhinitis frequently coexist. Rhinitis symptoms have been reported in up to 94% of asthma patients and asthma has been reported among 19–38% of those with allergic rhinitis [1]. Allergic rhinitis is considered an independent risk factor for developing asthma [2].

Patients with allergic rhinitis exhibit increased eosinophil activity in both upper and lower airways, suggesting common inflammatory features [3].

Chawes et al. [4] found a consistent association between upper and lower patency and an inverse relationship between nasal patency and eosinophil count in

blood and at nasal level. Circulating Th2 effector cells in an allergic rhinitis model proved to be responsible for promoting lower airways inflammation [5].

Both injection and sublingual immunotherapy may reduce the risk of developing asthma in children with allergic rhinitis [6].

To date several aspects of airways-related allergic pathology remain controversial because of the relatively recent institution of rigorous experimental research on the hyperactivity of the immune system. Of these, the most disquieting and worthy of mention is the epidemiological evolution, not only on account of the important increase recorded in the last decades of the twentieth century, but also as a result of the difficulty in finding reliable medium- and long-term follow-up studies. In fact, although there is an

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international agreement on the increase of the prevalence of allergic rhinitis in recent decades, data emerging from various studies appear to be widely dishomogeneous. For example, values relative to childhood vary, in different studies, between 1.3% and 52%. Even taking into consideration specific social-geographic realities, the results of different studies appear contradictory and suspended between negation and assertion of an increased prevalence within the last decade.

Major problems justifying the difficulties encountered in this kind of epidemiological research are, essentially: use of general rather than specialist medical data, differences existing among the examined subgroups of populations, annual variations of incidence of this pathology, times of distribution and gathering in of questionnaires, and accuracy of diagnosis [7].

An important concept is that the level of upper airways impairment represents a major determinant in the development of lower airways complications. In this sense, recent epidemiological studies in the general population have effectively confirmed that rhinitis and asthma are associated with each other, the first representing a strong risk factor for the development of the latter [8–10].

In view of the lack of long-term follow-up studies focused on the analysis of these very important aspects of the airways-related allergic pathology, the present study had the objective of following the epidemiological and clinical evolution of allergic rhinitis in three different territorial areas of Central Italy in the last 20 years and highlighting the efficacy of different treatments in the prevention of complications and specifically the development of asthma.

Material and methods

Between September 1980 and January 1981, we screened 1620 children attending 7 state schools (4 elementary and 3 lower secondary) for allergic rhinitis. The different locations (urban, suburban, and rural areas) of chosen schools allowed us to consider heterogeneous environmental conditions, and to compare epidemiological aspects relative to the rural environment (the Rome hinterland) with those related to suburban residential areas (existence of gardens) and to central areas of the city of Rome (scarce presence of green areas). A questionnaire was handed out to collect an accurate clinical history. The presence of significant data such as family history of allergy, chronic or periodic rhinitis possibly associated with conjunctivitis, nasal itching, sneezing, asthma, and food and medication allergy was highlighted.

All children underwent a skin test on the inner forearm. Allergens tested were chosen from among

those most commonly responsible for nasal allergy in Central Italy: Gramineae (*Holcus lanatus* and *Cynodon dactylus*), Composites (*Artemisia vulgaris*), *Parietaria officinalis*, and *Dermatophagoides pteronyssinus*.

Children with positive skin test results went on in the study. Specifically they underwent the following examinations: objective examination of nasal mucosa, broncho-pneumologic evaluation, examination of nasal secretion and levels of secretory immunoglobulins, active anterior rhinomanometry, determination of blocking antibodies according to the methods proposed by Deuschl et al. [11], mucociliary transport time determination by using a colored indicator (mixture of charcoal powder and 3% saccharin), dosage, using the radioallergosorbent test (RAST), for specific IgEs.

In addition, radiological examination of paranasal sinuses in the four standard projections was performed and three degrees of lesion were defined (first degree, darkening; second degree, thickening of the mucosa; third degree, polypoid degeneration).

To analyze the development of long-term complications and the long-term efficacy of different therapies, positive skin test patients were examined yearly for a period of 32 years. Specifically, each patient underwent ear, nose, and throat objective examination, active anterior rhinomanometry, and mucociliary transport time determination once a year in the same seasonal period. A targeted questionnaire was also filled with the examiner to carefully evaluate the yearly presence of complications. Specifically, we considered as complications of allergic rhinitis the development of rhinosinusitis (sinusal inflammation without purulent secretion and without systemic reaction), rhino-otitis (otitis media due to eustachian tube dysfunction), bronchitis or asthma.

Only data regarding patients who completed the follow-up (46 of 73 patients) are discussed in the present study. The remaining 27 patients moved from their original location during the follow-up period, and thus were exposed to different environmental conditions with the risk of contamination of the results. For this reason we decided to exclude them from the study. From an analysis of the above-mentioned parameters, we divided the sample into three classes: patients who exhibited an improvement of their symptoms or a normalization of nasal resistance to physiologic values (defined as 'recovered'), patients in whom symptoms and objective parameters remained or returned to a pretreatment level (defined as 'unchanged'), and patients in whom complications developed (defined as 'complications'). The study was approved by the Scientific Committees of Rome and Siena Universities. Data underwent statistical analysis using chi-squared test.

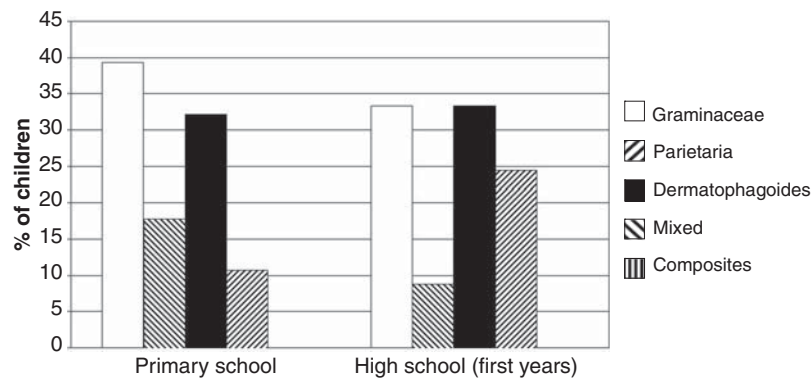


Figure 1. School level and positivity to allergens.

Results

In all, 73 children reacted positively to skin tests (4.5%). No skin positivity to Composites alone was identified, being exclusively present in the mixed forms; positivity to Graminaceae or to Dermatophagoides was found to be clearly higher among children at lower secondary schools; finally, positivity to *Parietaria officinalis* was most common among elementary schoolchildren (Figure 1). In the rural area, positivity to Dermatophagoides was the prevailing result; in the suburban area we noted the sharing of this primacy between Graminaceae and Dermatophagoides, while in the urban area reaction to Graminaceae prevailed (Figure 2).

Values of nasal secretory immunoglobins did not diverge from the norm, neither did they differ significantly in relation to school level or to area of origin. From an examination of rhinomanometric values it emerged that elementary schoolchildren living in the rural area had better nasal patency than other examined subgroups. Values of the titers of blocking antibodies were found to be within the normal range (0.16 nitrogen units (NU)/ml) in more than 80% of children at both school levels and in different areas. Moreover, elementary schoolchildren showed better mucociliary clearance than lower secondary

schoolchildren (mean mucociliary transport time: 11.1 min vs 14.2 min).

As regards radiological images, in elementary schools 53.6% of cases did not present lesions, that were in any case limited to first degree in 35.7% of children. In lower secondary schools only 22.2% of images appeared normal, with 44.4% classifiable as first degree lesions, 26.6% as second degree lesions, and 6.6% as third degree lesions (Figure 3).

Concerning the relationship between sinusal radiological lesions and skin positivity (Table I), a prevalence of first degree lesions was found, with children positive to Graminaceae showing the lower number of pathological images; third degree lesions were found only in association with sensitization to Dermatophagoides. In the rural area 60% of children showed second degree lesions, in the suburban area quite a uniform distribution of different radiological images was noted, while in the urban area first degree lesions prevailed (Figure 4). Furthermore, it should be underlined that more than half of subjects without clinical symptoms presented first or second degree radiological lesions.

The RAST examination was carried out on 30 of the 73 skin test-positive children for whom their parents' permission was obtained for further investigations. The RAST was clearly positive only in those

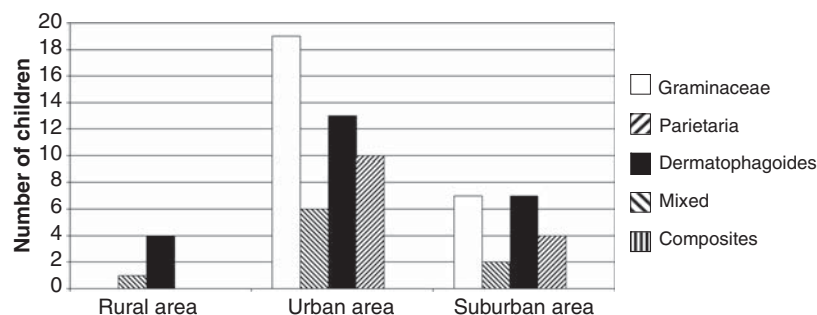


Figure 2. Living areas and positivity to allergens.

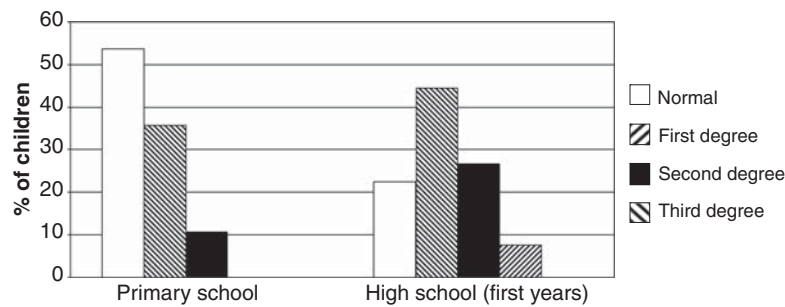


Figure 3. School level and radiological images.

subjects having third degree radiological lesions, evident symptoms, and strong skin reactions.

Concerning treatments administered, 21 patients had not received any treatment, 15 were treated with symptomatic drugs (systemic antihistaminics and/or topical corticosteroids, stopping the treatment when a subjective relief was obtained), 10 received systemic immunotherapy for the first 3 years consecutively, moreover, after 3 years of treatment they used symptomatic drugs when needed.

Following the evolution of the disease in the three groups over the years (Table II), we noted that patients who received symptomatic drugs exhibited the maximum of relief starting from the third to the eighth year of follow-up, with 13 of 15 patients reporting an improvement of symptoms; immunotherapy achieved the best efficacy starting from the sixth to the tenth year (8 of 10 patients recovered). Subsequently, improvements decreased, in the two groups, to a steady level of 11 of 15 and 6 of 10 recovered patients, respectively.

On the contrary, patients who were not treated exhibited, for the entire follow-up period, an improvement of symptoms in just a few case (4 or 5 patients out of 21).

Focusing on complications, we found that therapeutic abstention implied a progressive development of local or lower airways pathologies such as rhinitis, rhinosinusitis, bronchitis or asthma, the first two cases appearing after just 2 years of follow-up; in

this group the number of complications progressively increased to 11 after 12 years of follow-up. On the contrary, in the group treated with symptomatic drugs only two complications developed: one case of rhinitis after 6 years and one case of rhinosinusitis after 10 years of follow-up. Moreover, patients receiving immunotherapy did not exhibit any complications during the whole follow-up period. Obviously all patients exhibiting complications received the appropriate treatment for those acute episodes; moreover, asthmatic patients were followed by a bronchopneumologist starting from when asthma developed.

At the end of the study, 21 of 46 subjects were found to be without any allergic symptom at the nasal level; for 12 of 46 the situation appeared unchanged, 10 of 46 had developed pathologies of the lower respiratory tract, rhino-otitis or rhinosinusitis, and 3 of 46 had become asthmatic (Table III).

Specifically, outcomes among groups were as follows. Patients who did not receive any kind of treatment exhibited a remission of symptoms in 4 of 21 cases, a stability of the disease in 6 of 21 cases, and the development of complications in 11 of 21 cases, comprising 8 cases with rhinosinusitis or rhino-otitis and 3 cases of asthma. In the group treated with symptomatic drugs we highlighted a recovery in 11 of 15 patients, stability of symptoms in 2 of 15, and complications in 2 of 15. Finally, patients who had undergone immunotherapy considered their symptoms improved in 6 of 10 and stable in 4 of 10 ($p < 0.005$) (Figure 5).

Table I. Relationship between radiological lesions and skin test positivity.

Allergen/skin positivities	Radiological image			
	Normal	First degree lesion	Second degree lesion	Third degree lesion
Parietaria ($n = 9$)	3	5	1	—
Dermatophagoides ($n = 24$)	4	11	6	3
Graminaceae ($n = 26$)	12	8	6	—
Mixed ($n = 14$)	6	6	2	—
All allergens ($n = 73$)	25	30	15	3

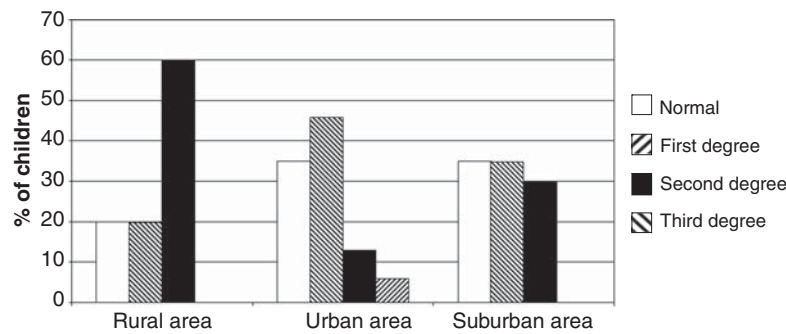


Figure 4. Living areas and radiological images.

Discussion

An analysis of results obtained from the initial screening gave a percentage of allergic subjects of 4.5%, whose distribution by age and living environment enabled us to see some epidemiological logic. In fact children living in the rural area, due to the fact that they are constantly exposed to pollens, showed a lower incidence of seasonal allergic forms and a higher positivity to *Dermatophagoides* (80%). While positivity to *Parietaria* was more frequent (17.8%) in elementary schoolchildren, multiple skin responses were more widespread (24.4%) in lower secondary schoolchildren. Elementary schoolchildren showed lower degrees of skin positivity, better nasal patency, more efficient nasal clearance, and less frequent anomalous radiological findings. Such data suggest the evolving character of nasal allergic pathology, calling for an early diagnosis and adequate treatment. In this context, pinpointing the main risk factors in relation to children’s living area contributes to the adoption of preventive environmental measures and to the institution of an appropriate therapeutic protocol. The present study showed an increased prevalence of allergic rhinitis in the last 20 years of the

twentieth century, with a jump from 4.5% to the present level of 10–20%; however, only a greater international effort aimed at recording the natural history of the hyperactive pathology in various geographic, social-economic, and hygienic-health contexts will lead to definitive conclusions about the epidemiological course of allergic rhinitis. Focusing on the second target of our study, as we have already noted, many clinical and experimental trials suggest a strong immunological and functional relationship between nose and bronchi. For example, a study by Rachelefsky [12] demonstrated that children with combined sinusitis and lower airways hyperactivity showed a significant improvement of their lower airways symptoms after an appropriate medical treatment of sinusitis. Moreover, nasal stimulation can induce bronchoconstriction by the rhino-bronchial reflex and inflammatory mediators originating from the nose could trigger bronchial inflammation. According to these and to our data, the concept: ‘one airway, one disease,’ in the field of rhinitis–asthma relationship, acquires a strong rationale. In this sense, we believe that it is extremely important to stress that among our patients, asthma, the most dangerous and invalidating complication of

Table II. Evaluation of the evolution of the disease over the years.

Treatment	Outcome	No. of patients per year															
		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	13th	14th	28th	29th	30th	32nd
Symptomatic drugs (15 patients)	Recovered	8	8	10	12	13	12	13	12	11	11	11	10	10	10	11	11
	Unchanged	7	7	5	3	2	2	1	2	3	2	2	3	3	3	2	2
	Complications	0	0	0	0	0	1	1	1	1	2	2	2	2	2	2	2
Immunotherapy (10 patients)	Recovered	3	3	4	4	5	6	6	8	8	8	6	5	6	6	6	6
	Unchanged	7	7	6	6	5	4	4	2	2	2	4	5	4	4	4	4
	Complications	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No treatment (21 patients)	Recovered	4	5	5	5	4	5	6	4	4	5	4	4	4	4	4	4
	Unchanged	17	14	14	14	12	11	11	11	10	7	6	6	6	6	6	6
	Complications	0	2	2	2	5	5	6	6	7	9	11	11	11	11	11	11

Table III. Outcome after 32 years of follow-up.

Outcome	No. of children/total population
Recovered	21/46
Unchanged	12/46
Complications	10/46
Asthma	3/46

Complications included rhinosinusitis, rhino-otitis, and bronchitis.

allergic rhinitis, developed only in the non-treated group. Even in patients presenting a negative evolution despite symptomatic treatment, the feared asthmatic complications never appeared.

According to the most actual literature allergic rhinitis often precedes the development of asthma because impaired nasal function affects the lower airways and systemic inflammatory mechanisms are involved in the clinical expression of the allergic airway syndrome [13].

According to Ciprandi and Capasso [14] allergic rhinitis duration and sensitization to house dust mites are associated with impaired spirometric values and could be considered prognostic markers of bronchial involvement in children with allergic rhinitis. Moreover bronchial hyperactivity is frequently seen in patients with chronic rhinitis and should be suspected in the presence of some risk factors, such as tree or mite sensitization, a duration longer than 5 years, and FEV1 values $\leq 86\%$ of predicted value [15].

Mahesh et al. [16] observed that both children and adults developed asthma within 2 years after the onset of rhinitis.

As regards the long-term efficacy of symptomatic drugs, in the present study the maximum efficacy was found after 3 years of follow-up. The efficacy decreased after 8 years of follow-up and the first case of complication developed after 6 years of follow-up.

As regards the long-term efficacy of immunotherapy, the maximum of efficacy was demonstrated after

6 years of follow-up. A moderate decrease of efficacy was seen after 10 years of follow-up and no cases of complication developed during the whole follow-up.

In the patients that had received no treatment a significant worsening of the symptoms was found after 2 years of follow-up and the first case of complication developed after 1 year of follow-up.

According to our study, asthma developed only in non-treated patients.

Trying to understand which factors could act as adjuvants, we may suppose that some environmental factors influence the pathogenesis of allergic rhinitis, enhancing the so-called allergic march from nasal allergy to bronchial asthma.

Lee et al. [17] examined the trend of asthma, allergic rhinitis, and eczema prevalence in school-children aged 6–7 years in Hong Kong from 1995 to 2001 using standardized ISAAC methodology. There were 4448 and 3618 children participating in 2001 and 1995, respectively. The prevalence of lifetime rhinitis (42.4% vs 38.9%, $p < 0.01$), current rhinitis (37.4% vs 35.1%, $p < 0.03$), current rhinoconjunctivitis (17.2 vs 13.6%, $p < 0.01$), and lifetime eczema (30.7% vs 28.1%, $p = 0.01$) increased significantly.

From January 2006 to December 2006, Hsu et al. [18] enrolled 1368 children, attending 12 elementary schools located in the 6 districts in Taipei. The incidence of allergic rhinitis in the study was 50.1%. Factors such as gender ($p < 0.001$), parity ($p < 0.05$), carpets ($p < 0.025$), and air pollution ($p < 0.001$) increased risk. Other potential factors such as low birth weight, maternal age at childbirth, parental education, gestational complications, presence of tobacco smokers, and exposure to pets and molds did not significantly increase the risk of developing allergic rhinitis.

The role of passive smoking for allergies and asthma in children above the age of 3 years was evaluated by Keil et al. [19] in a prospective multicenter birth cohort study with 1314 recruited children in

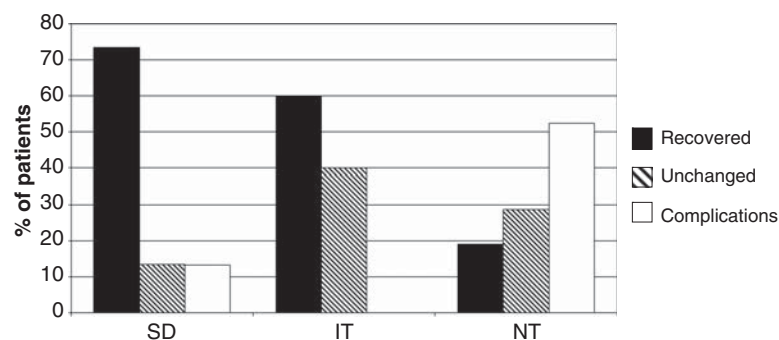


Figure 5. Relationship between treatment and outcome. IT, immunotherapy; NT, no treatment; SD, symptomatic drugs.

Germany. During the first 10 years, 18% of the children were exposed to regular maternal smoking since pregnancy, 43% to irregular maternal or only paternal smoking. The results suggest that regular maternal smoking is a strong risk factor for allergic sensitization and asthma symptoms during the first 10 years of life, but only in children with allergic parents.

The role of epigenetic control in the onset of allergic diseases was investigated by Shinohara [20] in a retrospective cohort study, involving 400 pairs of mothers with physician-diagnosed allergic rhinitis and their offspring (aged 7–18 months). Offspring whose mothers had any allergic rhinitis symptoms during early pregnancy showed a significantly higher adjusted odds ratio for the onset of allergic rhinitis. The authors suggested the presence of possible epigenetic mechanisms regulating the onset of allergic rhinitis in humans, presumably through increased organ-specific hypersensitivity.

In more recent studies progression from allergic rhinitis to rhinosinusitis was suggested as linked to patients with particular anatomic-clinical conditions (i.e. infraorbital cells, frontal intersinus cells or comorbid asthma). These could, according to the authors, be associated with faster development of chronic rhinosinusitis in patients with allergic rhinitis, assuming that the presence of these alterations could identify patients who should be counseled on compliance with medical therapy for allergic rhinitis [21].

Pistiner et al. [22] examined the relationship between mode of delivery and the development of atopy and allergic diseases among 432 children with a parental history of atopy followed from birth to age 9 years. Their findings suggested that cesarean delivery was associated with allergic rhinitis and atopy among children with a parental history of asthma or allergies. This could be explained by lack of contact with the maternal vaginal/fecal flora or reduced/absent labor during cesarean delivery. The hypothesis that cesarean section might increase the risk of allergic diseases was not confirmed by Park et al. [23]: according to the latter authors, depriving the newborn of exposure to maternal vaginal microflora may not be associated with the subsequent development of asthma, allergic rhinitis, or atopic dermatitis in Korean children.

Data on the association between breastfeeding and allergies are conflicting too. Tanaka et al. [24] studied the relationship between the duration and exclusivity of breastfeeding and the prevalence of wheeze, asthma, and eczema in Japanese children. Data indicated that exclusive breastfeeding for 4 months or more was associated with a lower prevalence of asthma.

In 2012, Calderon et al. [25] published a statement for pediatric immunotherapy for the EAACI in which

several recommendations were stated for researchers, physicians, and pharmaceutical industries; moreover they conclude that immunotherapy is safe and effective on pathology progression to asthma and it should be started early in the disease process even in children with well-controlled allergic symptoms.

Another 10-year follow-up study published by Jacobsen et al. in 2007 [26] concluded that specific immunotherapy has long-term clinical effects and the potential for preventing development of asthma in children with allergic rhinoconjunctivitis up to 7 years after treatment termination.

Conclusions

On the basis of the data we obtained in 32 years of follow-up (the longest period ever published), we can conclude that the use of immunotherapy guarantees, in a large number of patients, remission of local symptoms and valid protection against local and bronchial complications as also reported in recent studies. The sublingual/oral administration, proposed at the end of the 1980s, represents the most relevant step forward of this therapy, from the point of view of both efficacy and compliance, making specific immunotherapy the most appropriate approach to allergic rhinitis in the majority of cases [27].

Symptomatic treatment with antihistaminics and/or corticosteroids, although not always able to interrupt the natural history of allergic rhinitis, represents an extremely valid therapeutic weapon, and it is always to be preferred to abstention from any treatment that exposes patients to ear, sinus, and/or tracheal-bronchial complications.

The present study seems to confirm the evidence of the atopic march from allergic rhinitis to asthma when there is a lack of early treatment of the nasal impairment.

Specific allergen immunotherapy for seasonal allergic rhinitis reduces the risk of developing asthma [2].

Our conclusion is that early intervention may change the natural course of allergic rhinitis, preventing the progression to asthma.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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